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Original Articles

Absorption of Radioactive Vitamin B_{12} After Total Gastrectomy 161
James A. Halsted, Marvin Gasster and Ernst J. Drenick

Adrenocortical Function and 17-Hydroxycorticosteroids in Pernicious Anemia 169
Avery A. Sandberg, Kristen Eik-Nes, Don H. Nelson, J. G. Palmer, G. E. Cartwright and M. M. Wintrobe

Treatment of Subacute Thyroiditis with Cortisone 174
Robert C. Hunter, Jr., and Daniel J. Sheehan

Special Article

Hospital Survey and Construction Program in Massachusetts 177
A. Daniel Rubenstein

Medical Progress

ACTH and Cortisone Therapy of Rheumatic Fever and Rheumatic Carditis (To be continued) 183
Benedict F. Massell

Medical Intelligence

Annular Pancreas Producing Duodenal Obstruction in Infancy 191
Wilfred T. Small and Carroll Z. Berman

By the London Post 193
John Lister

Case Records of the Massachusetts General Hospital . . 195

Editorials

Surgical Pilgrimage 204
Federal Aid and Hospital Construction . . . 205
The Drowning Season 205

Massachusetts Medical Society 205
Civil Defense Agency 206
Notices xi

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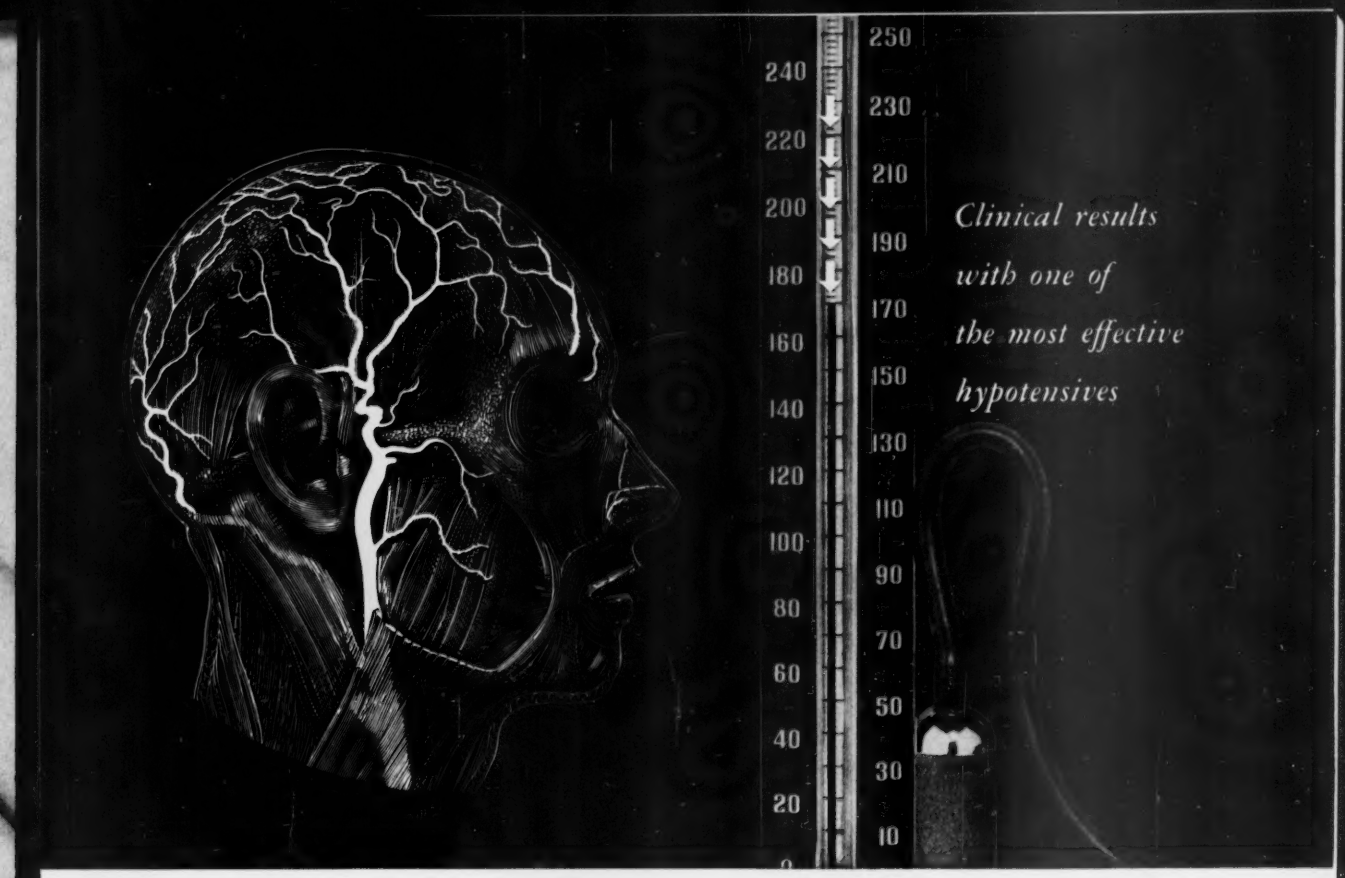

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1. Moyer, J. H.; Miller, S. I., and Ford, R. V.: J.A.M.A. *152*:1121 (July 18) 1953.
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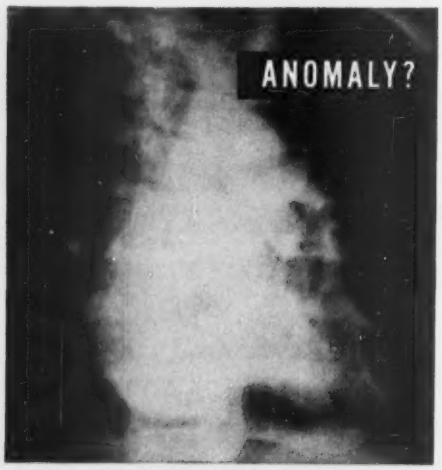

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Volume 251 JULY 29, 1954 Number 5

ABSORPTION OF RADIOACTIVE VITAMIN B_{12} AFTER TOTAL GASTRECTOMY*

Relation to Macrocytic Anemia and to the Site of Origin of Castle's Intrinsic Factor

JAMES A. HALSTED, M.D.,† MARVIN GASSTER, M.D.,‡ AND ERNST J. DRENICK, M.D.§

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TWENTY-five years ago Castle[1] showed that the oral administration of normal gastric juice mixed with beef muscle to patients with pernicious anemia resulted in a hematologic response, although neither substance was effective by itself. This led to the concept that pernicious anemia is caused by deficiency of a gastric or "intrinsic factor" that normally reacts with an "extrinsic" or food factor to produce a substance necessary for hematopoiesis. The intrinsic factor was found to be present not only in normal human gastric juice but also in the intestinal and gastric mucosa of other animal species, particularly swine.[2] Since 1929 a controversy has existed about the site of origin of the intrinsic factor in man. Evidence to date indicates that in swine it is produced principally in the pyloric end of the stomach and in the duodenum,[3] but that in man it is produced principally in the fundus of the stomach.[4] It is in this part of the stomach that degenerative changes can be demonstrated histologically in pernicious anemia.[5] The question remains whether, in man, there is any source of intrinsic factor outside the stomach itself. One of the arguments advanced in favor of secretion of intrinsic factor in the Brunner glands of the duodenum in man, as it is in the hog, is that pernicious anemia does not appear to develop in all patients who have had a total gastrectomy; yet one might expect this to happen invariably if the entire source of intrinsic factor had been surgically extirpated. The observations reported below bear on this question of the site of origin of the intrinsic factor.

In 1948 vitamin B_{12} was discovered, and this is now known to be the extrinsic or food factor necessary for normal hematopoiesis. Pernicious anemia results from a deficiency of available vitamin B_{12}. This deficiency is not dietary in origin since the patient presumably ingests the trivial requirement of 1 microgm. a day in his food. Furthermore vitamin B_{12} is synthesized by bacteria in the intestinal tract, and the feces of patients with pernicious anemia contain as much vitamin B_{12} as those of healthy persons.[6] This amounts to fifty to two hundred and fifty times the daily requirement of the vitamin. Since, in pernicious anemia, bacteria occur high up in the gastrointestinal tract, where absorption chiefly occurs, one would expect that ample amounts of vitamin B_{12} would be available provided it could be absorbed. Castle[7] has stated:

> . . . this disease would not develop if the patient could effect daily the transfer of a millionth of a gram of vitamin B_{12} the distance of a small fraction of a millimeter across the intestinal mucosa and into the blood stream. This he cannot do, principally as a result of failure of his stomach to secrete into its lumen some essential but still unknown substance.

The function of this essential substance, the intrinsic factor, appears to be that of enabling vitamin B_{12} to be absorbed into the body across the intestinal membrane. The way in which it exerts this function and its exact chemical nature are as yet unknown.

Oral administration of vitamin B_{12} to patients with pernicious anemia is usually without effect unless extremely large doses are given.[8] However, it has been shown that when as little as 10 cc. of normal gastric juice was administered orally with only 1 microgm. of vitamin B_{12} daily a measurable hematologic effect occurred.[9] Fractionation procedures designed to obtain purer preparations of intrinsic factor from stomach mucosa have been carried out in several laboratories. Materials have been prepared that have physiologic activity in amounts as little as 2 mg., as measured by the hematopoietic response of a patient with pernicious anemia given the fraction orally with vitamin B_{12}. This is the only method that has so far

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From Wadsworth General Hospital, Veterans Administration Center, and the Department of Medicine, School of Medicine, University of California Medical Center.

Supported in part by gifts from the Upjohn Company, Kalamazoo, Michigan, and Merck and Company, Incorporated, Rahway, New Jersey.

†Associate clinical professor of medicine, University of California Medical Center; chief, Gastroenterological Section, Veterans Administration Center.

‡Resident in gastroenterology, Veterans Administration Center.

§Staff physician, Veterans Administration Center.

been available to assay the activity of intrinsic-factor preparations. However, since there is evidence that the function of intrinsic factor is to promote absorption of vitamin B_{12} it should be possible to determine activity of these preparations by measurement of the absorption when the vitamin is administered orally with them. Because bacterial synthesis results in the formation of vitamin B_{12} intestinal absorption cannot be measured by subtraction of the amount present in feces from a known quantity given orally. However, since vitamin B_{12} contains cobalt as an essential ingredient of the molecule it is possible to produce radioactive vitamin B_{12} by the use of cobalt^{60} in its synthesis.[10] This can be detected in minute amounts in the feces, owing to intense gamma emission of isotopic cobalt, by means of the sensitive scintillation counter. Although cobalt^{60} has a half life of five and three-tenths years the minute amounts that can be used in the tracer technic are considered safe.*

Heinle and his associates,[11] in 1952, first demonstrated that patients with pernicious anemia failed to absorb cobalt^{60}-labeled vitamin B_{12} as measured by fecal excretion of this substance. They found that 4 patients excreted 75 to 95 per cent of an oral dose of 0.5 microgm. When a source of intrinsic factor was added to the test dose excretion ranged between 5 and 29 per cent in several tests. Callender, Turnbull and Wakisaka[12] reported similar findings.†

In 1953 Swendseid, Halsted and Libby[14] showed that patients with total gastrectomy behave in similar fashion to those with pernicious anemia so far as absorption of orally administered cobalt^{60}-labeled vitamin B_{12} is concerned. Four such patients excreted from 86 to 100 per cent of a 0.5-microgm. dose. When gastric juice was given with the vitamin B_{12} only 6 to 18 per cent was recovered in the stools. Since this report data on the absorption of vitamin B_{12} in 7 additional patients have been obtained. The clinical significance of these findings in relation to the development of macrocytic anemia in patients who have had a total gastrectomy is discussed below, and reasons are given that may explain its failure to develop in all such patients.

Methods

Cobalt^{60}-labeled vitamin B_{12} (hereafter referred to as radioactive vitamin B_{12}) with a specific activity of 92 microgm. per milligram was first used; 0.5-microgm. doses, each containing 0.046 microcurie of the isotope, were administered. Each day's stool output was collected in a separate cardboard container lined with waxed paper. It was then transferred to a porcelain crucible and evaporated to dryness in the steam bath. Subsequently, it was ashed at 500° C. for six to twelve hours in a muffle furnace. The ash was then transferred to an ointment tin, made up to a constant volume of 20 cc. by the addition of water, and the gamma rays were counted in a scintillation counter. Recovery experiments demonstrated no loss of cobalt^{60} by ashing at 500° C. for twelve hours.

Stools were collected for five days, and the radioactivity present in each day's stool was counted after processing by the method described above. Radioactivity was nearly always absent or negligible by the fourth day. The total amount present in the specimens was then accumulated for the result of total excretion.

During the latter part of the investigation more sensitive counting apparatus was obtained, and radioactive vitamin B_{12} with a specific activity of 220 microgm. per milligram was available.‡ This enabled the use of 0.5-microgm. doses of Co^{60}-labeled vitamin B_{12} each containing 0.110 microcurie of radioactivity. With the more sensitive scintillation counter and the more active vitamin we were able to count the radioactivity present in each day's stool without the cumbersome technic of drying and ashing each specimen. Each stool was collected in a quart ice-cream container, and water added to a volume of 400 cc. This was then homogenized by a motor-driven stirring rod for ten minutes. By this method as little as 0.002 microcurie of radioactivity (2 per cent of the administered dose, could be accurately counted.§

There are certain unavoidable errors in this method. A small error, probably not greater than 3 per cent, is inherent in the counting technic. Additional sources of error occur through carelessness on the part of the patient and through possible losses in transfer of the stools. If, in any case, doubt arose regarding possible loss of a stool, or a significant part of one, the test was discarded.

Clinical Material

Eleven patients subjected to total gastrectomy two months to seven years previously were studied. The operation was done for carcinoma in 9, for leiomyosarcoma of the stomach in 1 and for benign ulcer in 1.

Control experiments were conducted by the administration of 0.5-microgm. doses of radioactive vitamin B_{12} to 11 control subjects. These persons were without anemia or known pernicious anemia that had been treated, and each had an intact gastrointestinal tract. Tests were also made in 7 patients with proved pernicious anemia who were treated and in remission, and in 3 with idiopathic achlorhydria.

Because the detailed clinical course and the data obtained in the study of each patient with total gastrectomy are pertinent to the findings relative to the absorption of vitamin B_{12}, each patient's history is

*United States Atomic Energy Commission Authorization No. 17055.

†Schilling[13] reported a method of determining intrinsic-factor activity by detection of urinary radioactivity. After giving a test dose of the radioactive vitamin orally he injected a "flushing" dose of 1000 microgm. of nonradioactive vitamin B_{12}. Radioactivity appearing in the urine indicated absorption of the vitamin. Without this flushing dose no radioactivity could be detected in normal subjects, or in patients with pernicious anemia given intrinsic factor.

‡We are indebted to Merck and Company, Rahway, New Jersey, for generous supplies of radioactive vitamin B_{12}, through the co-operation of Dr. Charles A. Rosenblum.

§We wish to thank Dr. Raymond L. Libby, Dr. Franz K. Bauer and Dr. Benedict Cassen of the Radioisotope Unit, Veterans Administration Center, for guidance and many helpful suggestions in the technical aspects of isotope problems.

summarized in the following protocols, and the clinical data are given in Table 1.

CASE 1. G.S., a 44-year-old man, had a total gastrectomy on April 10, 1947, for carcinoma of the stomach. The esophagus was transected above the cardioesophageal junction, and the duodenum was divided just beyond the pylorus. An end-to-side esophagojejunostomy was performed. At operation no ulcer was present, but an indurated, ulcerating lesion was present high up on the lesser curvature. One regional lymph node revealed metastatic carcinoma. Before operation 35 units of free hydrochloric acid was found, and there was no anemia. Ever since the operation he has received injections of liver extract and vitamin B_{12} at regular intervals, as well as capsules containing folic acid. His weight was 150 pounds before the operation but has never been more than 120 pounds since. He has had frequent attacks of diarrhea, and examination of the stools has demonstrated increased amounts of fat. A fat-balance study in the metabolic ward in 1953 disclosed excretion of 11 gm. of fat daily on a diet containing 71 gm. of fat (14 per cent). On March 13, 1953, a sternal-marrow aspiration showed a completely normal bone marrow. On January 11, 1954, the red-cell count was 4,450,000, the hematocrit 44 per cent, and the hemoglobin 15.0 gm. per 100 cc.

CASE 2. J.F.M., a 64-year-old man, had a total gastrectomy on November 20, 1947, for carcinoma of the stomach, which consisted of 2 malignant adenomas. He had lost 25 pounds in weight. The esophagus was divided above the cardia, and the duodenum transected just beyond the pylorus; an esophagojejunostomy with enteroenterostomy was performed. Before the operation he had no free hydrochloric acid after histamine stimulation, and there was no anemia. No metastases were found at operation. Since then he has been well but has not regained his normal weight (he weighed 165 pounds before the 1st symptoms of illness, and since operation his weight has been constant at 129 pounds). He has received injections of vitamin B_{12} at regular intervals since 1951, and had been given liver extract before that time. In February, 1954, a sternal-marrow aspiration was entirely normal. The red-cell count was 4,380,000, the hemoglobin 15.0 gm. per 100 cc., and the hematocrit 43 per cent.

TABLE 1. *Clinical Data in 11 Patients after Total Gastrectomy.*

CASE NO.	AGE	DATE OF OPERATION	DATE OF VITAMIN B_{12} ABSORPTION STUDIES	DATE OF HEMATOLOGIC STUDIES	BONE MARROW	RED-CELL COUNT	HEMATOCRIT	HEMOGLOBIN	FREE HYDROCHLORIC BEFORE OPERATION	WEIGHT BEFORE OPERATION	WEIGHT AFTER OPERATION	MEDICATION
	yr.					*x10⁶*	*%*	*gm./100 cc.*				
1	44	4/10/47	Oct., 1953	Jan., 1954	Normal (Mar. 1953)	4.45	44	15.0	Present	150	120	Vitamin B_{12} or liver extract parenterally & folic acid orally, for several years
2	64	11/20/47	Feb., 1954	Feb., 1954	Normal	4.38	43	15.0	Absent	165	129	Liver extract before 1951 & vitamin B_{12} parenterally since then
3	58	9/18/51	Aug., 1953	Jan., 1954	Normal	3.60	34	13.4	Present	168	150	Vitamin B_{12} parenterally & folic acid orally since operation
4	63	11/26/51	Oct., 1953	Oct., 1953	Normal	5.01	46	14.5	Present	130	115	None
5	62	12/ 6/51	Jan., 1954	Dec., 1953	—	3.50	—	11.2	Present	188	164	Liver extract parenterally once per wk. since operation
6	62	5/12/52	Apr., 1953	Jan., 1953	Normal	3.40	34	12.0	(Not tested)	145	120	Vitamin B_{12} parenterally bi-weekly for 6 mo. after operation
7	32	7/14/52	Apr., 1953	Feb., 1954	—	4.90	47	15.0	Present	150	150	Vitamin B_{12} parenterally once per mo. & folic acid orally since operation
8	60	10/10/52	Oct., 1953	Oct., 1953	Normal	3.70	41	11.2	Absent	150	122	Liver extract; patient has had pernicious anemia since 1941.
9	58	12/13/52	Apr., 1953	Nov., 1953	Normal	4.20	40	12.8	Absent	150	134	4 injections of 15 microgm. of vitamin B_{12} in April and May, 1953
10	54	10/ 1/53	Dec., 1953	Feb., 1954	—	5.26	42	12.0	Present	200	166	Capsules containing folic acid for 1 mo. after operation
11	61	11/ 6/53	Jan., 1954	Dec., 1953	Normal	4.00	40	12.4	Present	180	140	None

CASE 3. F.G., a 58-year-old unemployed man, entered the hospital on August 27, 1951, complaining of epigastric pain and vomiting. X-ray examination revealed deformity of the duodenum, with evidence of pyloric obstruction. A gastric analysis demonstrated 90 clinical units of free hydrochloric acid. Operation on September 18 disclosed an irregular and indurated ulcer involving the antrum, which proved to be carcinoma. A total gastrectomy was carried out. The esophagus was divided above the cardia, and the duodenum was transected 3 cm. beyond the pylorus. The stomach, spleen and two thirds of the pancreas were removed. A segment of jejunum was interposed between the esophagus and the duodenal stump to act as a substitute stomach. No metastases were present.

Since the gastrectomy the patient has had mild diarrhea. In January, 1952, a fat-balance study showed that he excreted 36 gm. of fat daily on a dietary intake of 105 gm. of fat. A glucose tolerance test was normal. His weight has remained at 150 pounds; before the operation his normal weight was 168 pounds. On February 12 the sternal marrow was normal; the red-cell count was 3,170,000, and the hemoglobin 11.2 gm. per 100 cc. He was treated with

vitamin B_{12} parenterally and folic acid orally, with no change in the blood picture. On November 10 ferrous sulfate, 0.3 gm. 3 times a day, was started. Vitamin B_{12} and folic acid were stopped. On January 26, 1954, the sternal marrow was entirely normal. On March 15 the hemoglobin was 13.4 gm. per 100 cc., and the hematocrit 40 per cent. The improvement in the blood picture coincided with the administration of iron.

CASE 4. M.M., a 63-year-old man, entered the hospital on November 5, 1951, complaining of epigastric burning pain, with a weight loss of 11 pounds during the preceding 6 months. X-ray examination revealed a deformity on the greater curvature caused by extrinsic pressure. Physical examination showed a palpable mass in the upper abdomen, an enlarged spleen, but no enlarged lymph nodes. There was no anemia or abnormal white blood cells. Free hydrochloric acid was present on gastric analysis. On November 26 a total gastrectomy was performed. On exploration a hard spherical mass, 15 cm. in diameter, that arose in the greater curvature area of the stomach was encountered. This proved to be a leiomyosarcoma. Numerous regional lymph nodes were present but did not contain tumor. The esophagus was divided above the cardioesophageal junction, and the duodenum was divided just beyond the pylorus. The spleen and about half the pancreas were removed, and a segment of jejunum was interposed between the cut end of the esophagus and the duodenal stump, to act as a substitute stomach.

Postoperatively the patient had a stormy course, with several complications, from which he eventually recovered. He was discharged from the hospital on June 11, 1952. Since that time he has been essentially well although he has been unable to gain any weight, being 15 pounds below his level before operation. The stools have been consistently bulky, light colored and greasy. Sternal-marrow aspiration on October 19, 1953, revealed a completely normal bone marrow. The red-cell count was 5,010,000, the hematocrit 46 per cent, and the hemoglobin 14.5 gm. per 100 cc. He had had no injections of liver extract or vitamin B_{12} and no oral intake of folic acid or other vitamins.

CASE 5. E.S., a 62-year-old Negro, entered the hospital on September 18, 1951, because of anorexia and weight loss of 3 months' duration. X-ray and gastroscopic examinations suggested gastric carcinoma. The red-cell count was 4,000,000, the hemoglobin 12.6 gm. per 100 cc., and the hematocrit 41 per cent. Free hydrochloric acid was present on gastric analysis. On December 6 a total gastric resection with splenectomy was performed. The esophagus was divided just above the esophagogastric junction, and the duodenum was transected about 1 cm. distal to the pylorus. A jejunal segment was transplanted between the transected esophagus and duodenum. The lesion was an adenocarcinoma without demonstrable metastases.

The patient has remained fairly well since the operation, but has been constantly 25 pounds underweight. On February 9, 1954, the red-cell count was 3,670,000, and the hemoglobin 9.7 gm. per 100 cc. He has been given liver extract intramuscularly at weekly intervals ever since the operation. His stools were bulky and demonstrated increased fat on microscopical examination. With iron therapy the hemoglobin rose to 12.4 gm. per 100 cc. on March 12.

CASE 6. F.C.P., a 62-year-old man, was admitted to the hospital on April 28, 1952, with intermittent diarrhea, weight loss and anorexia of 4 months' duration. X-ray films revealed gastric lesion, which was considered malignant. Gastroscopic examination showed a fungating, ulcerative lesion. The hematocrit was 46 per cent, and the hemoglobin 15.0 gm. per 100 cc. On May 12 a total gastrectomy, as well as a splenectomy and partial pancreatectomy, was performed. The esophagus was transected 2 cm. above the cardia, and the duodenum divided 3.0 cm. beyond the pylorus. A loop of jejunum was interposed between the partially resected esophagus and duodenum, to act as a substitute stomach. The tumor was an ulcerating carcinoma, 5 cm. in diameter. One regional lymph node disclosed metastatic carcinoma.

Since the operation he has had 2 or 3 very bulky, greasy stools daily. His weight has remained at 120 pounds (25 pounds below his normal weight). In January, 1953, examination of the blood demonstrated a red-cell count of 3,400,000, a hematocrit of 34 per cent and a hemoglobin of 12 gm. per 100 cc. The bone marrow at that time was entirely normal. The patient was then given injections of 15 microgm. of vitamin B_{12} at bi-weekly intervals for 6 months, without any change in the blood picture. On November 16 ferrous sulfate was started in a dosage of 0.3 gm. 3 times a day. With this therapy he felt stronger, and the red-cell count increased from 3,580,000 to 4,220,000, and the hemoglobin from 10.8 to 13.2 gm. per 100 cc.; the hematocrit rose from 34 to 41 per cent.

CASE 7. W.V., a 32-year-old male factory worker, had a total gastrectomy for carcinoma of the stomach on July 14, 1952. The stomach, spleen and tail of the pancreas were removed. A jejunal transplant was interposed between the end of the esophagus and the stump of the duodenum. The duodenum was transected 3 cm. from the pylorus and the esophagus divided 2 cm. above the cardia. The tumor consisted of a hard mass occupying the antrum and was found to be Grade 2 adenocarcinoma. No metastases were found.

The patient had had indigestion for 4 years, and an x-ray examination on June 13 had revealed marked pyloric obstruction and a prepyloric ulcer. The contents aspirated from the stomach contained free hydrochloric acid. Before operation the hemoglobin was 15.4 gm. per 100 cc., and the hematocrit 46 per cent; 17 months after operation the hemoglobin was 15.8 gm. per 100 cc., and the hematocrit 45 per cent. The stools were normally formed, light brown, very bulky and greasy, but he had only 1 movement daily. He had regained his normal weight. His family physician had given him injections of vitamin B_{12} every month, as well as vitamin capsules that contained folic acid. On February 1, 1954, the hematocrit was 47 per cent, and the hemoglobin 15.0 gm. per 100 cc.

CASE 8. J.C.T., a 60-year-old man, had had proved pernicious anemia since 1941. In September, 1952, he entered the hospital because of epigastric pain. X-ray examination disclosed a gastric ulcer high on the lesser curvature. On October 10 a total gastrectomy was performed because at operation the lesion proved to be carcinoma. No metastases were found. The resection included 1.5 cm. of the lower esophagus and 1.5 cm. of the duodenum. The spleen, with 6 cm. of the tail of the pancreas, was removed, and a segment of jejunum interposed between the cut end of the esophagus and duodenum to act as a substitute stomach. The patient made a good recovery and received bi-weekly injections of liver extract during March and April, 1953. The stools were extremely bulky from excess fat. The bone marrow was normal in October, when the hematocrit was 41 per cent, the red-cell count 3,700,000, and the hemoglobin 11.2 gm. per 100 cc. Injections of 15 microgm. of vitamin B_{12} at bi-weekly intervals were started on January 1, 1954.

CASE 9. M.M.E., a 58-year-old man, entered the hospital on November 20, 1952, complaining of weight loss and indigestion. He had a long history of duodenal ulcer with a perforation 24 years previously. He had lost 30 pounds during the previous year, and achlorhydria after histamine stimulation was demonstrated shortly before operation. X-ray examination revealed a prepyloric ulcer. The hemoglobin was 12.4 gm. per 100 cc., and the hematocrit 37 per cent. The stools were positive for occult blood. On December 13 a total gastrectomy for carcinoma of the stomach was performed. The operation consisted of removal of the stomach with 1 cm. of esophagus, 3 cm. of duodenum as well as omentum, spleen and the tail of the pancreas. A segment of jejunum was interposed between esophagus and duodenal stump to act as a substitute stomach. The carcinoma was 5.5 by 4.5 cm., involving the greater curvature of the antrum. One regional lymph node contained carcinoma; no other metastases were found.

Eleven months after operation sternal-marrow aspiration was completely normal. The red-cell count was 4,200,000, the hematocrit 40 per cent, and the hemoglobin 12.8 gm.

per 100 cc. The stools were very bulky, light brown, foamy and greasy. The patient weighed 134 pounds (12 pounds more than his weight before operation but 16 pounds less than his normal weight). He had received 4 injections of vitamin B_{12} 6 months previously, but no folic acid or liver extract had been given.

CASE 10. M.E.S., a 54-year-old man, entered the hospital on September 20, 1953, because of melena. The hematocrit was 24 per cent, the hemoglobin 7.3 gm. per 100 cc., and the red-cell count 2,720,000. The stools were guaiac positive. Free hydrochloric acid was present on gastric analysis. X-ray films showed a large ulcer on the lesser curvature of the stomach in the antral region, with gastric retention. Bleeding continued, and on October 1 a gastric resection revealed carcinoma of the stomach. A total gastrectomy was attempted, but it was necessary to leave in situ approximately 1.5 cm. of the cardiac end of the stomach. The duodenum was transected 4.5 cm. beyond the pylorus. There were metastases to regional lymph nodes. The spleen and omentum were removed, and a jejunal segment interposed between esophagus and duodenum to act as a substitute stomach.

The patient made a good recovery. For 1 month after discharge he took multivitamin capsules, which contained, among other vitamins, folic acid and vitamin B_{12}. On February 5, 1954, the red-cell count was 5,260,000, the hematocrit 42 per cent, and the hemoglobin 12.0 gm. per 100 cc. Before operation he weighed 200 pounds; since the gastrectomy his weight has been constant at 167 pounds. The stools are bulky, light colored and greasy.

TABLE 2. *Fecal Excretion of 0.5 Microgm. of Cobalt^{60}-Labeled Vitamin B_{12} in Control Subjects.*

CASE NO.	AGE yr.	DIAGNOSIS	EXCRETION %
12	37	No disease	41
13	64	Arteriosclerosis	26
14	31	No disease	20
15	48	No disease	30
16	48	Hypogonadism	29
17	32	No disease	33
18	45	Obesity	45
19	51	Dystrophia myotonia	33
20	30	No disease	34
21	34	Reiter's syndrome	19
22	24	Rheumatoid arthritis	57

CASE 11. B.A., a 61-year-old man, entered the hospital on September 18, 1953, because of epigastric pain, nausea and a 25-pound weight loss during a period of 8 months. The hemoglobin was 14.6 gm. per 100 cc., and the hematocrit 42 per cent. The stools were guaiac negative. Free hydrochloric acid was present on gastric analysis performed on October 2. The bone marrow was completely normal. Numerous studies, including x-ray examinations of the stomach, small bowel and colon, disclosed no abnormalities. On November 6, at exploratory laparotomy, a large ulcer at the cardiac end of the stomach was found. Because the surgeon believed this to be a carcinoma, a total gastrectomy was performed, as well as a splenectomy, omentectomy and partial pancreatectomy. A jejunal transplant was anastomosed between the esophagus and jejunum. Histologically, the ulcer was benign.

The patient made a gradual recovery and feels well at the present time, except for constipation and inability to regain his former weight. Before his illness he weighed 180 pounds. Before the gastrectomy he weighed 150 pounds, and at present, 3 months after operation, he weighs 139 pounds. On January 20, 1954, the red-cell count was 4,000,000, the hemoglobin 12.4 gm. per 100 cc., and the hematocrit 40 per cent. The stools contained an excess of fat. During a 10-day period he excreted 21 gm. of fat daily on a weighed diet containing 72 gm. of fat.

RESULTS

Fecal excretion of 0.5-microgm. doses of radioactive vitamin B_{12} in the 11 patients who served as controls is presented in Table 2. The smallest amount excreted was 19 per cent and the greatest amount 57 per cent; the average for the group was 33 per cent. Further studies of vitamin B_{12} absorption in normal persons, as determined by this method, are in progress.

TABLE 3. *Fecal Excretion of 0.5 Microgm. of Cobalt^{60}-Labeled Vitamin B_{12} in Patients with Idiopathic Achlorhydria.*

CASE NO.	AGE yr.	EXCRETION %
23	43	20
24	48	51
25	58	34

The results of tests in the 3 patients with idiopathic achlorhydria are shown in Table 3. In each case there was histamine achlorhydria on repeated examination, and there was no anemia. Excretion of the radioactive vitamin in this group was 20, 34 and 51 per cent respectively, averaging 35 per cent, which is similar to that in the control group.

The results of excretion of the radiovitamin in 7 patients with pernicious anemia are presented in Table 4. It can be seen that practically all of it was excreted in each case. When a source of intrinsic factor, such as gastric juice in Cases 27, 29 and 30, or intrinsic-factor concentrate,* as in Case 32, was given simultaneously with the radioactive vitamin, fecal excretion

TABLE 4. *Fecal Excretion of 0.5 Microgm. of Cobalt^{60}-Labeled Vitamin B_{12} in Pernicious Anemia, with and without Concomitant Administration of Intrinsic Factor.*

CASE NO.	TEST DOSE OF VITAMIN microgm.	EXCRETION %
26	0.5	84
27	0.5	87
	0.5*	22
28	0.5	100
29	0.5	80 (Test 1)
	0.5	86 (Test 2)
	0.5†	60
30	0.5	100 (Test 1)
	0.5	97 (Test 2)
31	0.5	99 (Test 1)
	0.5	99 (Test 2)
	0.5*	38
32	0.5	100
	0.5‡	32

*Plus 100 cc. of gastric juice.
†Plus 110 cc. of gastric juice.
‡Plus intrinsic-factor concentrate.

*Kindly furnished by Dr. Elmer Alpert, Merck and Company, Incorporated, Rahway, New Jersey.

was significantly decreased. No attempt was made to give the same amount of gastric juice to each patient. In Case 29 the radioactive vitamin was not absorbed as well as in the other cases, possibly owing to the fact that the gastric juice administered had been stored long enough to result in reduced intrinsic-factor activity. With a source of intrinsic factor given with the radioactive vitamin the average excretion in the patients with pernicious anemia was 38 per cent, which is similar to the control and to the achlorhydria groups, whereas the average excretion without intrinsic factor was 93 per cent.

The clinical data obtained in the study of the 11 patients who had had a total gastrectomy are summarized in Table 1. It will be noted that the longest interval after operation was seven years in 2 cases. In each of the remainder it was less than two and a half years. No patient had a macrocytic anemia, with the exception of Case 8, who had had pernicious anemia for eleven years before operation. The bone marrow was normal in the 8 patients in whom it was examined. Free hydrochloric acid was present in 7 of 10 patients before the operation. All but 1 patient weighed significantly less than before the operation; the weight loss averaged 24 pounds. Eight patients had received liver extract or vitamin B_{12} parenterally in significant amounts, and folic acid had been given orally to 4 patients. The 2 patients who had received no therapy of this nature were operated on four and twenty-seven months before the time of this writing. One patient had received no therapy for a year. As may be noted in the case reports all but 1 patient had marked steatorrhea, which could be judged from gross inspection as a rule. Studies of fat balance were performed in 3 patients, who excreted 14, 34 and 29 per cent of fat intake, respectively.

Absorption studies (Fig. 1) demonstrated that every patient subjected to total gastrectomy excreted practically all the radioactive vitamin when it was given without intrinsic factor (gastric juice) but that when it was administered with gastric juice fecal excretion was greatly decreased. The average excretion of the test dose was 87 per cent in 16 tests when it was given alone but only 20 per cent in 14 tests when it was given with gastric juice—this was less than the average fecal excretion of the same test dose given to the controls.

The amount of gastric juice given to the 11 patients in 14 tests ranged from 50 to 175 cc. By the technics employed to date in this laboratory no definite correlation between the degree of fecal excretion and the amount of gastric juice used could be determined.

Discussion

It is assumed that the degree of fecal excretion of the radioactive vitamin is in inverse relation to the amount absorbed. No other explanation is readily conceivable. The possibility that the vitamin is absorbed and then re-excreted into the intestine via the bile is not tenable in the light of the considerable differences in excretion when intrinsic factor was given with it to the patients with pernicious anemia and those subjected to total gastrectomy, unless one assigns an entirely different function to intrinsic factor from that of enhancing intestinal absorption. Evidence so far accumulated indicates that this is its function. Although what is being measured in the radioactive technic is cobalt^{60}, not vitamin B_{12} itself, since cobalt is a firmly bound part of the molecule of the cobalamins (vitamin B_{12}), it is not likely that the cobalt part of the molecule could be split off in the intestine and the remainder absorbed.

The site of secretion of intrinsic factor has been a subject of controversy. That the stomach is the

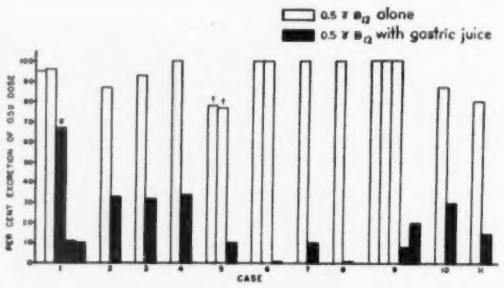

Figure 1. *Fecal Excretion of Cobalt^{60}-Labeled Vitamin B_{12} after Total Gastrectomy (Effect of Gastric Juice).*
**During this test severe diarrhea developed shortly after the dose was given. This may explain the high excretion.*
†During both these tests the stool collection was incomplete. The data are included because the result of the test with gastric juice is in such striking contrast.

only place in man where it is secreted has been suggested by experiments[15] in which juice obtained from the duodenum, which had been excluded from the pylorus by a balloon, was without intrinsic-factor activity. Paulson and his associates[16] found no intrinsic factor in duodenal juice after total gastrectomy. Although desiccated preparations of normal human duodenum had some intrinsic-factor activity, passive adsorption or active absorption of gastric intrinsic factor by the tissue could not be excluded.[17]

The results obtained in patients after a total gastrectomy indicate that they do not absorb orally administered vitamin B_{12}. All but one had steatorrhea, and all but 1 were unable to regain their average normal preoperative weight despite adequate caloric intake. Although these facts suggest a general defect in intestinal absorption such an explanation for the failure to absorb orally administered vitamin B_{12} is negated by the fact that the vitamin is absorbed in amounts even greater than in normal controls when a source of intrinsic factor is given simultaneously. It is to be noted that all but 4 patients had free hydrochloric acid, and thus presumably intrinsic factor, before operation. Only 1 (Case 8) had pernicious anemia before the gastrectomy was performed.

These observations, when considered in conjunction with the work of Heinle et al.[11] in pernicious anemia, and confirmed by us, indicate that the patient with a total gastrectomy does not absorb vitamin B_{12} because of a lack of intrinsic factor and, furthermore, that the stomach is the only site of secretion of the intrinsic factor in man.

The results obtained in the three patients with achlorhydria, who absorbed the radioactive vitamin normally, indicate that free hydrochloric acid is not a factor in the absorption of vitamin B_{12}. That these patients might later develop pernicious anemia is, of course, possible, since it is well known that achlorhydria may precede the onset of the disease by many years.

Since patients with either pernicious anemia or a total gastrectomy excrete all the radioactive vitamin but absorb it as normal persons do when a source of intrinsic factor is given simultaneously, two clinical applications are apparent. It is possible to use this method for establishing, as probably conclusive, the diagnosis of pernicious anemia in a patient who is suspected of having the disease and who has been treated with liver extract, vitamin B_{12} or folic acid. An example of the validity of the test was seen when a sixty-five-year-old man with repeated histamine achlorhydria and no anemia was tested with a 0.5-microgm. dose (the result of this test is not listed). The patient excreted 84 per cent. Initially, it was thought that he had idiopathic achlorhydria, but later a history of pernicious anemia diagnosed many years before was elicited. He had been receiving regular injections of vitamin B_{12} ever since.

The other possible clinical use is the assay of intrinsic-factor preparations. Patients with pernicious anemia in remission or with a total gastrectomy may be used, and the result may be obtained in five days. Such studies are now in progress in this laboratory.

It is known that anemia resembling pernicious anemia may develop after total gastrectomy, but this is by no means the invariable result. Since cases of combined-system disease, as well as the hematologic picture of pernicious anemia, have been reported after total gastrectomy[18] it seems probable that the anemia is the true addisonian type. Since the patients do not absorb any vitamin B_{12} from dietary sources, the question arises why macrocytic anemia does not always follow total gastrectomy. Four factors in the over-all situation may explain this paradox:

Survival after operation. Only within the past ten years has total gastrectomy been practiced extensively. The mortality is about 10 or 15 per cent, and survival more than three years after operation for carcinoma (the indication in nearly all cases) is about 20 per cent. In the past seven years 48 total gastrectomies have been performed at Wadsworth General Hospital, with a hospital mortality of 21 per cent. Fourteen patients are now alive, but only 4 of these were operated on more than three years ago. Thus, not many patients survive the operation long enough for a macrocytic anemia to develop.

Interval before development of macrocytic anemia. It is impossible to state exactly how long this interval is; there are undoubtedly wide individual variations. In pernicious anemia when therapy is stopped it has been reported that relapse may not occur for as long as three years, with variations of two to thirty-eight months.[19] This suggests that vitamin B_{12} may be stored in the liver for long periods. The daily human requirement is not more than 1 microgm. a day—or less than 0.5 mg. a year! Thus, it is conceivable that liver stores in the patient who has had a total gastrectomy may be sufficient for his needs for several years, as suggested by Sturgis and Goldhamer.[20]

MacDonald, Ingelfinger and Belding[21] reported 3 cases of total gastrectomy, in 2 of which a pernicious-anemia type of blood picture developed two and five years after operation; the third patient had received periodic injections of liver extract. These same authors reviewed the cases of macrocytic anemia of the pernicious-anemia type occurring after total gastrectomy. Of 46 cases of total gastrectomy anemia resembling pernicious anemia developed in 12. The anemia appeared four years or more after surgery in 9 and six months after cessation of liver therapy in 1.

Completeness of gastrectomy. In the performance of total gastrectomy it is sometimes technically difficult to excise the cardiac end of the stomach above the esophagocardiac junction, unless a transthoracic approach is employed; 1 or 2 cm. of cardia may be left behind, as was necessary in 1 of our cases (Case 10). Yet these cases may be considered as total gastrectomies and so reported. Since, in man, the cardia of the stomach has been found to be an active site of secretion of intrinsic factor[4] a small amount of cardia left in situ might secrete an amount of intrinsic factor adequate for normal utilization of vitamin B_{12} from dietary sources, even though in Case 10 this was not observed.

Prophylactic therapy. Probably the most important reason why only a minority of patients who survive the operation of total gastrectomy manifest a macrocytic anemia of the pernicious-anemia type is that antianemic preparations are so widely prescribed. Even if the surgeon does not advise this medication as prophylaxis we have found that most patients actually receive it from their own physicians. Since nearly all have some degree of malnutrition the physician is likely to prescribe multivitamin capsules, many of which contain folic acid, which would prevent macrocytic anemia at least for some time. Preparations are now available that also contain vitamin B_{12} and intrinsic factor. Letters were written to 16 medical centers to ascertain whether it is common practice to advise routine

prophylactic therapy after total gastrectomy; all but 3 reported that routine prophylactic therapy was not advised, which is also the situation in this institution. None of our 11 patients have macrocytic anemia, but 9 had in fact received prophylactic therapy from their own physicians.*

Thus, when one considers the small number of patients surviving the operation for more than three years and the widespread use of antianemic medications that would prevent the macrocytic type of anemia, it is not surprising that it eventually develops in only a few patients after total gastrectomy.

Summary

A method for determining intestinal absorption of vitamin B_{12}, first described by Heinle and his associates, is discussed. In this method fecal excretion of cobalt^{60}-labeled vitamin B_{12} is measured with a scintillation counter.

Eleven normal persons excreted, on the average, 33 per cent of 0.5 microgm. of orally administered radioactive vitamin B_{12}.

Three patients with idiopathic achlorhydria excreted, on the average, 34 per cent of a similar dose.

Seven patients with pernicious anemia excreted, on the average, 93 per cent in 10 tests, but when a source of intrinsic factor was administered with the test dose in 4 patients, fecal excretion was decreased to an average of 38 per cent.

Eleven patients who had had total gastrectomy excreted, on the average, 87 per cent in 16 tests. When a source of intrinsic factor was administered with the test dose an average of only 20 per cent was excreted in 14 tests.

The clinical data obtained in the 11 patients who had had total gastrectomy revealed that none had macrocytic anemia, 10 were significantly underweight, 7 had a normocytic anemia, 10 had steatorrhea and 9 had received therapy that would prevent macrocytic anemia.

Reasons are given that satisfactorily explain on clinical grounds why macrocytic anemia rarely follows total gastrectomy.

Evidence is presented that the site of origin of intrinsic factor in man is limited to the stomach.

*Recently a patient on whom total gastrectomy had been performed in 1948 for carcinoma, entered this hospital with severe macrocytic anemia. He had received no prophylactic therapy. A reticulocyte response of 34 per cent occurred on the sixth day of parenteral vitamin B_{12} therapy. Cobalt^{60} excretion was 95 per cent, but only 49 per cent was excreted when an intrinsic-factor concentrate was administered with the radiovitamin.

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ADRENOCORTICAL FUNCTION AND METABOLISM OF 17-HYDROXYCORTICOSTEROIDS IN PERNICIOUS ANEMIA*

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STRAUSS and Brokaw[1] recently reviewed and evaluated various clinical and metabolic changes in pernicious anemia. They concluded that "the occurrence of numerous manifestations of Addison's disease of the suprarenal capsule in Addisonian pernicious anemia in relapse suggest that functional adrenocortical insufficiency may be present in certain cases of this condition." It was pointed out that, in addition to certain clinical similarities between Addison's disease and pernicious anemia, there is indirect evidence of impaired adrenocortical function in pernicious anemia. Thus, patients with pernicious anemia were unable to conserve sodium chloride or excrete a water load rapidly; the oral glucose tolerance curves were flat; no significant fall in circulation eosinophils followed the intramuscular administration of ACTH; and urinary excretion of 17-ketosteroids was diminished. Strauss and Brokaw suggested that vitamin B_{12} may be necessary for proper function of the adrenal cortex.

With the development of a method for the accurate measurement of small amounts of 17-hydroxycorticosteroids in the blood[2] it has become possible to determine the levels of these corticosteroids in various clinical conditions. Previous studies[3] have shown that determination of the plasma 17-hydroxycorticosteroid levels can be used as a reliable index of adrenocortical function. The present study concerns the function of the adrenal cortex and the metabolism of 17-hydroxycorticosteroids in patients with pernicious anemia.

METHODS AND MATERIALS

Blood for the determination of 17-hydroxycorticosteroids was obtained shortly after admission to the hospital and at varying intervals thereafter. Most of the control samples were drawn between 8 and 9 a.m.

Determination of plasma 17-hydroxycorticosteroids, ACTH tests, eosinophil and differential leukocyte counts and other hematologic procedures were carried out by methods previously described.[4-7]

The same lot numbers of adrenal steroids were used throughout these experiments. The hydrocortisone (Compound F acetate) and the free alcohols of hydrocortisone for oral administration were given in the form of a suspension. Gastric juice was obtained from normal young males or from patients with peptic ulcers. When steroids were administered in gastric juice they were suspended in 150 cc. of gastric juice and given immediately to the subjects.

RESULTS

Relation of Plasma 17-hydroxycorticosteroids to Clinical Course

Table 1 shows representative plasma levels of 17-hydroxycorticosteroids and the pertinent blood findings in 8 cases of pernicious anemia in relapse and after vitamin B_{12} therapy. The mean plasma level of 17-hydroxycorticosteroids in normal subjects at 8 to 8:30 a.m. in our laboratory is 13 ± 6 microgm. per 100 cc. of plasma, with 95 per cent of the values falling within the range of 3 to 26 microgm.[8]

In Case 2 the levels of plasma 17-hydroxycorticosteroids were at the extreme limit of the normal range on two occasions (24 and 25 microgm. per 100 cc.). This patient had continued and severe angina pectoris at the time and subsequently died of myocardial infarction. Values at and above these levels have been observed regularly in patients dying of a variety of diseases and appear to be nonspecific.

Case 3 was febrile, disoriented and very agitated on admission and for the first few days thereafter. During this initial period the 17-hydroxycorticosteroid levels were high. In contrast to patients with established adrenal insufficiency, who show no measurable levels of circulating 17-hydroxycorticosteroids or are unable to increase their low levels in response to ACTH, this patient was admitted to the hospital in "critical" condition with elevated 17-hydroxycorticosteroid levels. As the clinical condition improved the plasma 17-hydroxycorticosteroid levels correspondingly fell to within the normal range. This response is typical of that observed in other critically ill patients with normal adrenal function in whom the process is reversible.

In all the other cases of pernicious anemia the levels of 17-hydroxycorticosteroids were normal, both during the height of relapse of the disease and after vitamin B_{12} therapy.

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Effects of Adrenal Steroids on the Cellular Elements

Figure 1 shows, for comparison, the changes in the white-cell counts and 17-hydroxycorticosteroid levels after the oral administration of 200 mg. of compound F acetate to a normal subject and to a patient with pernicious anemia in relapse. It is evident from these changes, as well as from previously published data,[6] that in normal subjects four to eight hours after the oral administration of 200 mg. of compound F acetate, a rise of 6000 to 7000 cells above the control number occurs in the total number of leukocytes, primarily owing to a neutrophilia. In addition the number of eosinophils, lymphocytes and monocytes drops more than 50 per cent from the control values after the oral administration of the steroids. In contrast the patients with pernicious anemia showed no significant increase in the total number of leukocytes and only small increments of neutrophils after the oral administration of compound F acetate. The drop in the number of lymphocytes was of normal magnitude (Fig. 1 and 2). The number of monocytes decreased more than 50 per cent (not shown in the figures).

TABLE 1. *Relation of Plasma 17-hydroxycorticosteroids to Hematologic Course of Patients with Pernicious Anemia.*

CASE NO.	DATA DURING RELAPSE BEFORE VITAMIN B_{12} THERAPY		DATA DURING HEIGHT OF RETICULOCYTE RESPONSE		DATA AFTER VITAMIN B_{12} THERAPY	
	VOLUME OF PACKED RED BLOOD CELLS	17-HYDROXYCORTICOSTEROIDS* *microgm./100 cc. of plasma*	RETICULOCYTES %	17-HYDROXYCORTICOSTEROIDS *microgm./100 cc. of plasma*	VOLUME OF PACKED RED BLOOD CELLS *cc./100 cc.*	17-HYDROXYCORTICOSTEROIDS *microgm./100 cc. of plasma*
1	22.0	9-11	11	22	43.0	7
2	18.0	16-19	23	24	35.2	15
3	25.0	26-43	23	16	50.0	11
4	29.0	7-14	18	14	53.0	11
5	9.0	8-20	25	8	38.6	12
6	19.0	13-17	28	7	45.4	18
7	17.2	7-14	30	8	50.0	13
8	16.0	13-17	29	10	42.8	17
Means	19.5	12-19	23	14	44.8	13

*Ranges of values before therapy.

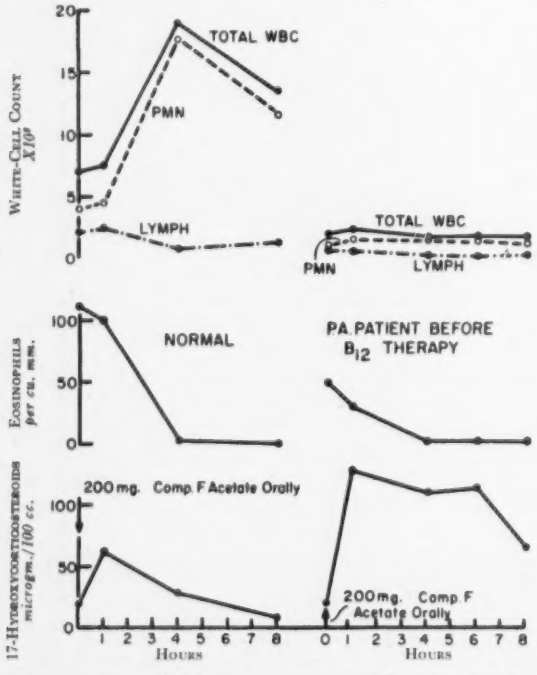

FIGURE 1. *Plasma 17-hydroxycorticosteroid Levels and Cellular Changes after the Oral Administration of Hydrocortisone Acetate to a Normal Subject and to a Patient with Pernicious Anemia in Relapse.*

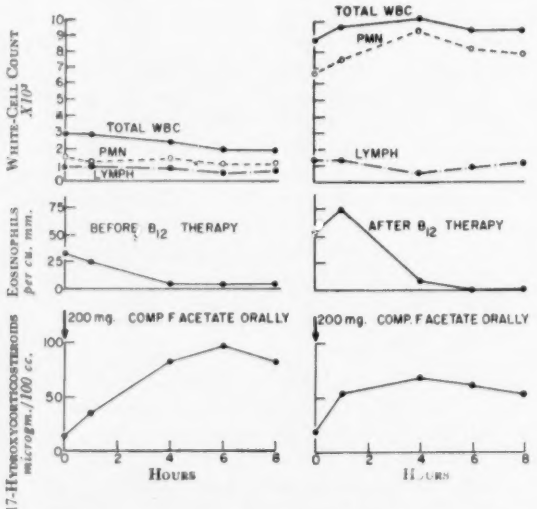

FIGURE 2. *Plasma 17-hydroxycorticosteroid Levels and Cellular Changes after the Oral Administration of Hydrocortisone Acetate to a Patient with Pernicious Anemia During Relapse and after Vitamin B_{12} Therapy.*

It is interesting that the eosinophil response to the oral administration of compound F acetate was normal (a decrease of more than 50 per cent) both before and after therapy (Fig. 2). Although the neutrophil response to the oral administration of hydrocortisone acetate tended to be greater after therapy, the rise was small when compared with that of normal young adults (Fig. 1).[6] No significant change occurred in the cells of the erythrocyte series.

Plasma 17-hydroxycorticosteroid Levels after Oral Administration of Adrenal Steroids

Figure 3 presents the plasma levels of 17-hydroxycorticosteroids after oral administration of 200 mg. of hydrocortisone acetate to patients with pernicious anemia and to normal subjects; it is evident that the levels were greatly elevated for prolonged periods in the former. Not only was the high level maintained but also the values at the peak concentration were higher in the patients than in the normal subjects in comparable experiments. The magnitude of the elevation of plasma 17-hydroxycorticosteroids after the ingestion of a test dose of hydrocortisone was not influenced significantly by treatment with vitamin B_{12}.

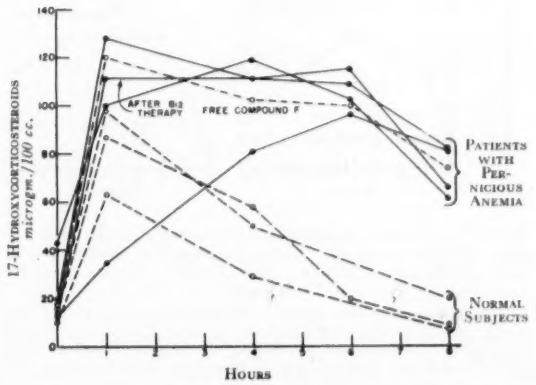

FIGURE 3. *17-hydroxycorticosteroid Levels in Plasma after the Oral Administration of 200 Mg. of Hydrocortisone Acetate to Normal Subjects and to Patients with Pernicious Anemia.*

Also shown are the plasma 17-hydroxycorticosteroid levels after the oral administration of the free alcohol of Compound F to a patient with pernicious anemia (dash-and-dot curve). Note the high levels reached and maintained in the plasma.

To test the hypothesis that patients with pernicious anemia are unable to remove the acetate radical by hydrolysis, either before or after the absorption of the ester, several patients were given the free alcohol of hydrocortisone (free Compound F) by mouth; no significant differences between the plasma levels of 17-hydroxycorticosteroids and those of the free alcohol of hydrocortisone were evident. A plasma 17-hydroxycorticosteroid curve similar to those in Figure 2 was observed eighteen months later when 200 mg. of free Compound F was administered orally to the same patient at a time when the pernicious anemia was in relapse.

Effects of ACTH on Plasma Levels of 17-hydroxycorticosteroids and White Cells in Patients with Pernicious Anemia in Relapse

After the intravenous infusion of ACTH for a period of six to eight hours, the rise in the levels of 17-hydroxycorticosteroids was normal in all 5 patients[7] (Fig. 4). Figure 5 shows the cellular changes and the plasma 17-hydroxycorticosteroid levels after the intravenous administration of ACTH to 2 of these patients. The changes in the remaining 3 were similar. In each the eosinophils decreased in number to the same extent as in normal subjects. This finding contrasts with that of Strauss and Brokaw.[1] Again, little neutrophilia was evident, although the number of lymphocytes and monocytes dropped significantly.

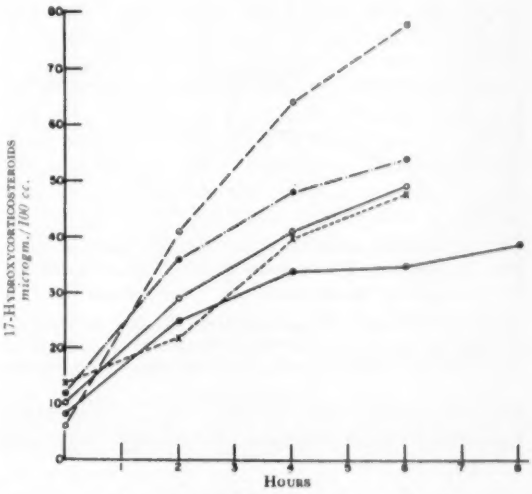

FIGURE 4. *Changes in the Plasma Levels of 17-hydroxycorticosteroids after the Continuous Intravenous Infusion of ACTH (25 International Units), over Periods of Six to Eight Hours, in 5 Patients with Pernicious Anemia in Relapse.*

The responses are similar to those seen in normal subjects.[7]

Plasma 17-hydroxycorticosteroid Levels after Intravenous Administration of Adrenal Steroids to Patients with Pernicious Anemia in Relapse

When it had been demonstrated that the adrenal cortex is capable of responding normally to the administration of ACTH the possibility remained that the metabolism of administered steroids was impaired in pernicious anemia. To test this hypothesis steroids were administered intravenously to several patients with pernicious anemia in relapse. The rate of disappearance of the corticosteroids from the plasma of patients with pernicious anemia was normal (Fig. 6).

Plasma 17-hydroxycorticosteroid Levels after Oral Administration of Adrenal Steroids to a Patient with Achylia Gastrica without Pernicious Anemia

Hydrocortisone acetate, 150 mg., was given orally to a twenty-five-year-old woman with achylia gastrica

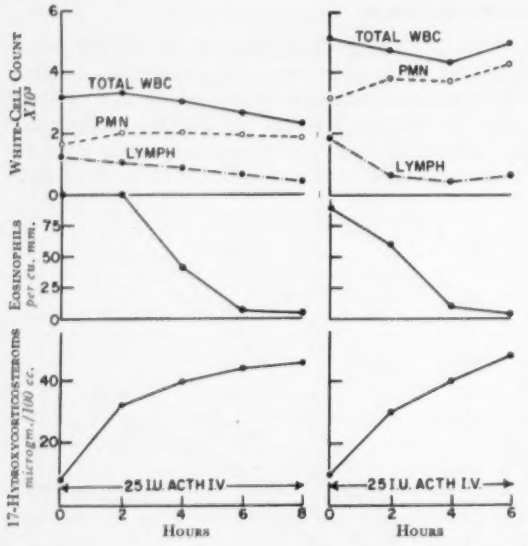

FIGURE 5. *Plasma 17-hydroxycorticosteroid Levels and Changes in Leukocytes after the Intravenous Administration of ACTH to 2 Patients with Pernicious Anemia in Relapse.*

but with no evidence of anemia (Fig. 7). This patient exhibited the same prolonged 17-hydroxycorticosteroid

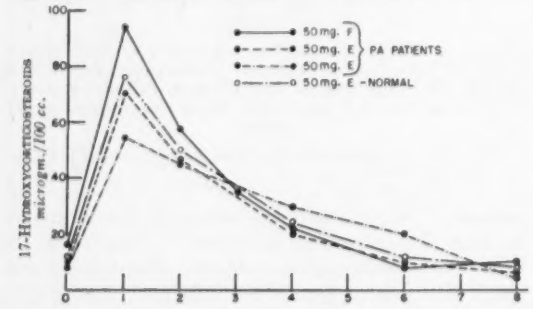

FIGURE 6. *Plasma 17-hydroxycorticosteroid Levels after the Intravenous Administration of the Free Alcohols of Hydrocortisone or Cortisone to Patients with Pernicious Anemia. The average levels in a normal subject are shown for comparison.*

plasma level after oral administration as the patient with pernicious anemia. Of interest is the considerable increase in the total number of leukocytes in this patient, in contrast to the small rise seen in patients with pernicious anemia.

Effects of Gastric Juice and Hydrochloric Acid on 17-hydroxycorticosteroids

Two patients with pernicious anemia, maintained in remission by treatment with vitamin B_{12}, were given 200 mg. of hydrocortisone acetate in 150 cc. of normal gastric juice. The 17-hydroxycorticosteroid levels were lower with than without gastric juice when the hydrocortisone acetate was administered (Table 2). Possibly, even lower levels would have been observed if more gastric juice had been given over a prolonged period.

To test its effect on ingested 17-hydroxycorticosteroids, gastric juice from normal subjects and from patients with peptic ulcer was incubated at 37°C. with 10 microgm. of hydrocortisone acetate for one

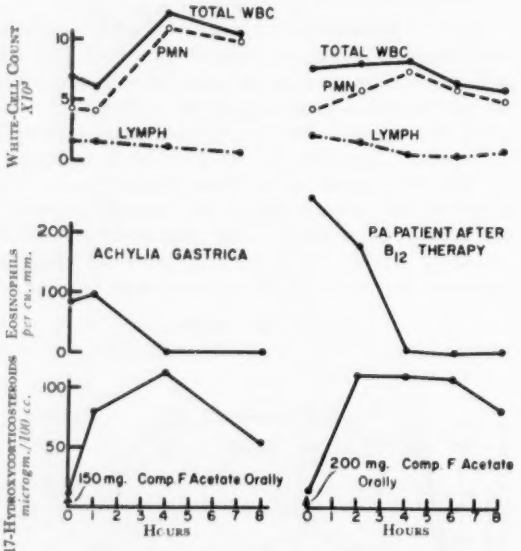

FIGURE 7. *Plasma 17-Hydroxycorticosteroid Levels and Cellular Changes after the Oral Administration of Hydrocortisone Acetate to a Patient with Achylia Gastrica and No Anemia.*

The changes in the plasma 17-hydroxycorticosteroids and leukocytes after the oral administration of Compound F acetate to a patient with pernicious anemia in remission are shown for comparison.

to twelve hours. After each incubation approximately 50 per cent (4 to 6 microgm.) of the original hydrocortisone acetate was recovered, indicating either that some (50 per cent) of the hydrocortisone acetate had been destroyed by the gastric juice or that it had been converted to a compound not measurable by our method. The amount of hydrocortisone acetate that disappeared after incubation for one hour (4 microgm.) was almost as large as that after incubation for twelve hours (6 microgm.). The incubation of hydrocortisone acetate with hydrochloric acid, in the pH range of normal gastric juice (pH 2 or 3), led to the destruction or disappearance of only 25 per cent (2 or 3 microgm.) of the steroid. Incubation with gastric juice from a patient with pernicious anemia led to only negligible loss of hydrocortisone acetate (1 to 1.5 microgm.), which was comparable to the 10 per cent lost when the steroid was incubated with water (1 microgm.).

Discussion

We have found no evidence that adrenocortical function is impaired in patients with pernicious anemia in relapse. This is indicated by the normal levels of 17-hydroxycorticosteroids during relapse and the ability of the adrenal cortex to respond normally to administered ACTH. That these patients metabolize steroids normally is evidenced by the normal disappearance from the plasma of intravenously administered cortisone or hydrocortisone and the normal response of the eosinophils in the patients with pernicious anemia. In a few of the patients with pernicious anemia in relapse the levels of 17-hydroxycorticosteroids were elevated; this occurred during the time that they were very ill and under considerable stress.

Table 2. *Plasma 17-hydroxycorticosteroid Levels after the Oral Administration of Hydrocortisone Acetate (200 mg.), with and without Normal Gastric Juice, to Patients with Pernicious Anemia in Remission.*

Interval After Steroid Administration *hr.*	Plasma 17-hydroxycorticosteroid Level	
	with gastric juice *microgm./100 cc.*	without gastric juice *microgm./100 cc.*
0	3	8
1	79	129
4	77	114
6	41	100
8	27	57
0	7	7
1	77	87
2	83	103
4	92	174
6	74	63
8	52	45

Since, in all probability, the spontaneous elevation of 17-hydroxycorticosteroid levels in the plasma during stress depends on a normally functioning adrenal cortex, the spontaneous elevation of these levels in patients with pernicious anemia in relapse may be regarded as additional evidence that adrenocortical function is not impaired in pernicious anemia.[3]

Vitamin B_{12} does not seem to play a significant part in the metabolism of 17-hydroxycorticosteroids. This is borne out by the fact that there were no demonstrable differences in the metabolism of these steroids after the patients had improved clinically and a normal hematologic status had been restored after therapy with vitamin B_{12}.

In each of the patients given ACTH intravenously a decrease in the number of eosinophils in excess of 50 per cent of the control level was observed. These findings are at variance with those of Strauss and Brokaw.[1] The discrepancy may be due to the fact that most of the patients described by them had been given ACTH by the intramuscular route; even in normal subjects the number of eosinophils may fail to drop after the intramuscular administration of ACTH.[9] It is noteworthy that 2 of the patients discussed by Strauss and Brokaw[1] who failed to respond with a significant decrease in eosinophils after intramuscular injection of ACTH showed a profound drop when the ACTH was given intravenously.

It is apparent from the data that, although the curves of plasma 17-hydroxycorticosteroids after intravenous administration of the free alcohols of either Compound F or E were comparable in patients with pernicious anemia and in normal subjects, there was a marked disparity between the two groups when the steroids were administered orally.

The curve of the plasma levels of 17-hydroxycorticosteroids merely serves as a graphic representation of the arithmetical sum, at several intervals over a given period, of the cumulative effects of those factors tending to increase the level (namely, endogenous supply and absorption from the gastrointestinal tract) and those tending to decrease the level (namely, utilization, catabolism and excretion). The intravenous tests demonstrate that the latter factors are the same in patients with pernicious anemia and in normal subjects since the curves of plasma 17-hydroxycorticosteroids were similar when the experimental conditions circumvented the variables of absorption and exogenous supply. Therefore, if metabolism of the 17-hydroxycorticosteroids is accepted as being the same in patients with pernicious anemia and in normal persons, the abnormal curves in the former after oral administration must be attributed to factors of absorption from the gastrointestinal tract. The rapidity with which very high levels of 17-hydroxycorticosteroids were attained after oral administration of hydrocortisone in patients with pernicious anemia testifies to the adequacy of absorption. Since the administered oral dose of the steroids was the same as in the normal subjects one is led to the conclusion that normal persons destroy much of the administered steroid before it is absorbed. Patients with pernicious anemia either do not destroy the steroid or do so to a much lesser extent. The data derived from the study of the patient with achylia gastrica without pernicious anemia indicate that the presence of achylia per se, rather than its metabolic effects, is the important factor in the response. Failure of vitamin B_{12} therapy to modify the results further implicates the achylia. Lastly, the in vitro tests indicate that normal gastric juice destroys the 17-hydroxycorticosteroids or changes them to a form that our analyses do not detect.

It follows, then, that the plateau seen in the curves of the patients with pernicious anemia after oral administration of 17-hydroxycorticosteroids is due to continuing absorption of undestroyed steroid from the gastrointestinal tract. In normal subjects, on the other hand, one would assume that there is no undestroyed corticosteroid remaining to be absorbed after the first hour or two.

Some comments may be made regarding the cellular changes induced by 17-hydroxycorticosteroids and ACTH in patients with pernicious anemia in relapse or remission. In most normal subjects the administration of adequate doses of ACTH or 17-hydroxycorticosteroids (cortisone or hydrocortisone) results in a brisk elevation of the total white-cell count, mainly owing to the rise in the neutrophilic leukocytes.[6] A decrease in the number of lymphocytes, monocytes and eosinophils also takes place. It was interesting that the usual decrease (over 50 per cent) in the number of lymphocytes, monocytes and eosinophils occurred in patients with pernicious anemia, whether they were in relapse or remission. On the other hand, the total white-cell count did not rise significantly in patients in relapse; very little neutrophilia occurred. This may be explained by failure to produce or to mobilize neutrophilic leukocytes normally. That there is a profound disturbance in neutrophil formation in pernicious anemia is indicated by the large size and multisegmentation of the neutrophilic leukocytes and the neutropenia seen in relapse. After vitamin B_{12} or liver therapy some rise in the neutrophils followed oral or intravenous administration of hydrocortisone, but the response was not of normal magnitude, indicating that some abnormality persisted. Likewise, it is to be noted that the morphologic abnormalities often do not disappear completely in "remission." The administration of hydrocortisone produced no changes of any significance in the erythrocyte series, either when the patient was in relapse or after vitamin B_{12} therapy.

Summary and Conclusions

Plasma 17-hydroxycorticosteroid levels were measured in patients with pernicious anemia in relapse and found to be within the normal range.

Adrenocortical function is not impaired in patients with pernicious anemia in relapse, as judged by the changes in the plasma 17-hydroxycorticosteroids after ACTH administration. Except for the lack of significant neutrophilia, patients with pernicious anemia show the usual changes in the leukocytes after ACTH or hydrocortisone administration.

After the oral administration of steroids, patients with pernicious anemia maintain higher levels of 17-hydroxycorticosteroids for longer periods than normal subjects do. Evidence is presented that normal subjects destroy large amounts of orally administered corticosteroids in the gastrointestinal tract before absorption, whereas patients with achylia gastrica do not.

The absence of neutrophilic response to ACTH or hydrocortisone administration in patients with pernicious anemia is further evidence of the disturbance in neutrophilic leukocyte production or release that is characteristic of this disease.

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TREATMENT OF SUBACUTE THYROIDITIS WITH CORTISONE*

Lieutenant Colonel Robert C. Hunter, Jr., MC, USA,† and Colonel Daniel J. Sheehan, MC, USA‡

ONE of the fields of usefulness for ACTH and cortisone is in the treatment of certain acute, self-limited inflammatory or allergic disorders, in which discomfort or even disability may be relieved by suppressive doses.[1] There are indications that subacute thyroiditis may be one of these diseases. Data to prove this point are difficult to assemble since the disease is uncommon and its course variable. We have found reports of 15 cases of subacute thyroiditis,[2-9] to which we have added 3 of our own, all with favorable response to ACTH and cortisone (Table 1). We did not find any reports of unfavorable results. Traut[10] described the onset of thyroiditis in a patient on prolonged cortisone treatment for rheumatoid arthritis, but the fluctuation of the gland and the normal radioiodine uptake indicated that this was probably the acute suppurative variety of thyroiditis.

During a period of three months we had the opportunity of treating 3 patients with cortisone for subacute thyroiditis. The results are summarized in Figure 1.

Case Reports

Case 1. A 32-year-old woman was admitted to the hospital on October 15, 1953, with a chief complaint of sore-

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ness in the neck. Six weeks previously she had noted the gradual onset of headache, malaise, nervousness and easy fatigability. About 2 weeks later she began to have chills, fever (maximum temperature of 103°F.), pain in the anterior portion of the neck and dysphagia severe enough to make the swallowing of water difficult. Two weeks before admission an enlarged thyroid gland was found, and a diagnosis of subacute thyroiditis made. She was treated with penicillin, oxytetracycline and sulfisoxazole, without benefit. She had lost 18 pounds by the time of admission.

TABLE 1. *Summary of Reports of ACTH and Cortisone Therapy in 18 Cases of Subacute Thyroiditis.*

SOURCE	NO. OF PATIENTS	AGENT	REMARKS
Krupp et al.[2]	1	Cortisone	Symptoms subsided in 36 hr.
Rowe et al.[3]	1	Cortisone & ACTH	Good immediate & fair late results; intermittent treatment for 1 yr.
Crile & Schneider[4]	3	Cortisone	Symptoms relieved within 4 hr.
	1	ACTH	
Lasser[5]	1	Cortisone	Symptoms relieved after 2d dose
Kahn et al.[6]	2	Cortisone	Symptoms cleared in 24 hr.
Clark et al.[7]	3	Cortisone	Marked relief apparent within 24 hr.
Teitelman & Rosenberg[8]	1	Cortisone	Prompt response to cortisone on both occasions when administered
Kinsell[9]	2	Cortisone	Evidence of acute inflammatory involvement of gland subsided promptly
Present series	3	Cortisone	Symptoms subsided in 4 to 48 hr.

Physical examination showed a diffuse, somewhat soft enlargement of the thyroid gland, which was markedly tender. The overlying skin was reddened.

The temperature was 99.4°F., the pulse 120, and the sedimentation rate 38.

The patient was given divided doses of cortisone by mouth, 200 mg. daily for 2 days and then 100 mg. daily. Within 24 hours of the first dose she became asymptomatic. After 7 days of treatment the thyroid gland was smaller, firmer and only slightly tender. She was discharged from the hospital still on a dose of 100 mg. of cortisone a day. On the 12th day of treatment she had a mild recurrence of fever and pain, with concurrent increased swelling and tenderness in the thyroid gland. The dosage was increased to 125 mg. daily, and the symptoms subsided in 48 hours. The drug was gradually decreased and eventually discontinued after 26 days of treatment. The thyroid gland was still slightly enlarged, but this cleared a few days after completion of treatment. Three months later there was no evidence of recurrence, and she had regained her lost weight. The total dose of cortisone was 3.3 gm.

CASE 2. A 39-year-old woman was admitted to the hospital on November 14, 1953, with a chief complaint of pain in the right side of the neck. About 6 weeks before admission she had noted the onset of an aching pain in the right side of the face. There was an associated malaise and tendency to tire quickly. Her dentist filled several cavities without relieving the pain. One week after the onset she began to have fever (temperature of 100 to 101°F.) each evening. The pain then became localized in the right side of the neck, and there was a mild dysphagia. She was examined several times during the next few weeks, but it was not until 1 week before admission that a mild enlargement and tenderness of the thyroid gland was found. She had lost 7 pounds in weight during the illness.

Physical examination showed the right lobe of the thyroid gland to be tender, firm and enlarged to a mass 3 by 4 cm. The isthmus and left lobe were slightly swollen and tender.

The temperature was 100°F., the pulse 110, and the sedimentation rate 44.

Treatment was initiated on the day after admission, with cortisone by mouth in divided doses, 300 mg. the 1st day, 200 mg. on the 2d and 100 mg. daily thereafter. The symptoms subsided before the 2d dose was administered. The thyroid swelling and tenderness disappeared within 48 hours. The patient was discharged from the hospital on a dose of 100 mg. of cortisone daily. After 12 days of treatment the drug was discontinued. Two days later the fever, malaise and pain recurred, and the thyroid gland became

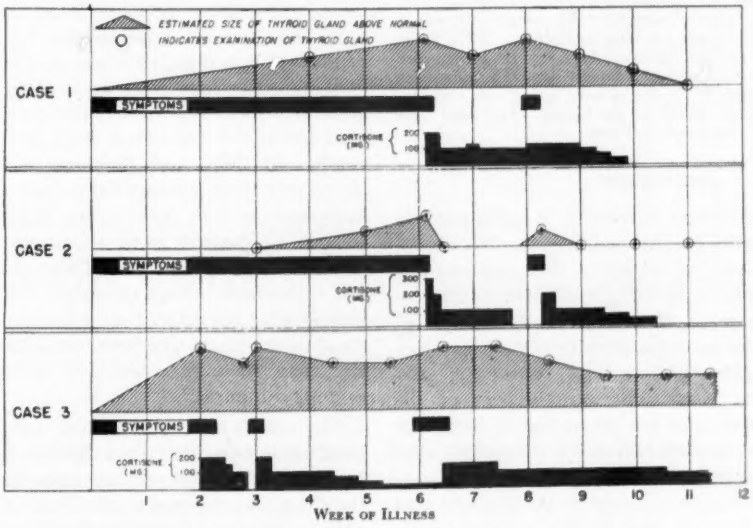

FIGURE 1. *Effect of Cortisone in 3 Cases of Subacute Thyroiditis.*

swollen and sore. Cortisone was again administered, 200 mg. a day initially and then in decreasing doses until it was discontinued 2 weeks later. Again, all the symptoms cleared before the 2d dose of cortisone was given. The thyroid gland was not examined until 5 days after cortisone was started, when it was normal. During the 2 months after the 2d course of cortisone the patient regained her lost weight, and there was no evidence of recurrence. The total dose of cortisone was 2.8 gm.

CASE 3. A 25-year-old Japanese war-bride was admitted to the hospital on December 26, 1953, with chief complaints of swelling and pain in the anterior portion of the neck. She gave a history of a sore throat that had started 2 weeks previously, with a rapid increase in severity causing marked difficulty in swallowing. There was associated nervousness, malaise, fever and anorexia with a weight loss of 8 pounds. Each evening she had shaking chills, and soaking sweats occurred about 3 times a night.

Physical examination showed a diffuse enlargement of the thyroid gland to several times its normal size. It was indurated and very tender.

The temperature was 98.4°F., the pulse 106, and the sedimentation rate 50.

Treatment with cortisone, 300 mg. daily by mouth in divided doses, was immediately begun. The symptoms subsided in 48 hours. The gland remained large and firm but lost most of its tenderness. The cortisone was gradually reduced and then stopped after 6 days of treatment. The temperature rose to 101°F., and the malaise, night sweats and local symptoms and findings in the thyroid gland returned. After 1 day cortisone was started again, 200 mg. daily. Within 24 hours, her symptoms were under control. The patient was maintained on this dosage for 2 days and then discharged from the hospital on a dose of 100 mg. daily. Two weeks later, this had been reduced to 25 mg. a day. She was still asymptomatic, but the thyroid gland remained firm and was only slightly smaller. After 4 days on this low dose all the symptoms returned in their original severity. The dosage was again increased, this time to 150 mg. daily, and again control was attained in 24 hours. This dosage was continued for 1 week, and then 100 mg. was given daily for 2 weeks. At that time, 7½ weeks after the beginning of cortisone therapy, the thyroid gland was distinctly smaller, and the major portion of the swelling was in the right lobe; it remained nontender. At the time of the last examination, 9½ weeks after treatment was started, the gland had not changed in total size, but the major portion of the swelling was in the isthmus and pyramidal lobe, which measured 3.5 by 4.5 cm. There were no local symptoms, chills, fever or sweats, but the patient believed that she tended to tire slightly more easily than was normal for her. The cortisone dosage was then down to 75 mg. a day, and it was contemplated that this therapy would be continued. The total dose of cortisone to that point was 6.8 gm.

DISCUSSION

The cause of subacute thyroiditis is unknown. It has many features suggesting an infection. No organism has been isolated although a viral etiology has been proposed. The involved gland shows characteristic changes consisting of increased fibrosis, loss of colloid and infiltration with polymorphonuclear leukocytes, lymphocytes, plasma cells, histiocytes and foreign-body giant cells. The arrangement of the histiocytes and giant cells has given rise to the name of giant-cell or pseudotuberculous thyroiditis, but there is no caseation and the cause is not thought to be tuberculosis. Crile and Rumsey[11] pointed out that the foreign-body reaction may be due to colloid from ruptured follicles.

The disease has a predilection for adult females. The onset may be abrupt or insidious, and in some cases is preceded by a respiratory infection. The symptoms are malaise, easy fatigue, fever, with a temperature as high as 105°F., pain in the neck and often visible swelling of the thyroid gland. The systemic symptoms may precede the local findings.[12] The pain may be localized to the thyroid gland or may be referred to the ear or face. Dysphagia may be present. The physical findings are fever, tachycardia and the enlarged, firm and tender thyroid gland. The sedimentation rate is nearly always increased, but leukocytosis is not usual. The radioiodine uptake is characteristically lowered to a negligible level. The basal metabolic rate and the serum protein-bound iodine are normal, and there is little to indicate either increased or decreased thyroid activity. The disease is self-limited, lasting from two weeks to six months or more, the average being two or three months.[13] There are no sequelae, and it is generally agreed that thyroid function is unimpaired after the disease.

The diagnosis can be made with some accuracy on the basis of the typical history and physical findings[14] but is easily missed in a patient complaining chiefly of pain in the ear, sore throat or dysphagia. Subacute thyroiditis is considered distinct from acute suppurative thyroiditis, struma lymphomatosa (Hashimoto) and struma fibrosa (Riedel). Needle biopsy of the gland has been advocated for doubtful cases.[15] When only one lobe is involved the disorder may be confused with thyroid adenoma or carcinoma, but the fever, tenderness and tendency to migrate to the other lobe usually serve to distinguish subacute thyroiditis.

By and large treatment has been unsatisfactory. Antibiotics have been completely ineffective,[16] although they have probably been used more extensively than any other treatment. Surgery is contraindicated in a benign, self-limited disease of this type. Striking remissions after irradiation of the thyroid gland have been reported, particularly from the Cleveland Clinic,[11,17] but others have not attained similar results. St. John and Nicholson,[13] for example, believed that their patients did as well with bed rest and analgesics as with irradiation. King and Rosellini[18] treated 10 patients with thiouracil and obtained a fairly rapid remission in 8. Other workers have been less enthusiastic about thiouracil compounds.[13] Robbins and his associates[19] used thyroid-stimulating hormone with results that were considered more impressive than those obtained with either x-ray therapy or propylthiouracil.

Our results in 3 cases treated with cortisone closely paralleled those described in the literature, with a prompt initial response but immediate relapse when the drug was stopped early (Table 1). The remarkable uniformity of the results obtained in these diverse reports indicates that cortisone in all probability is capable of altering the course of subacute thyroiditis beneficially. The small number of cases so far presented, as well as the lack of controls, precludes

a more positive conclusion. Because of the relapses when the cortisone was decreased or stopped too early and the necessity for prolonged treatment in some cases, we believe that this therapy is primarily suppressive; at least there is no good evidence at present that cortisone shortens the course of subacute thyroiditis.

The optimum dosage of cortisone and the duration of treatment are likewise undetermined. It appears that the minimum is about 100 mg. daily for two weeks, and the maximum varies with the individual case.

It is possible that the effect of cortisone would be potentiated by the addition of other types of therapy, such as bed rest. None of our patients received treatment besides cortisone, but all 3 were hospitalized for five to nine days at the beginning of treatment. Bed rest was not prescribed, but the patients obtained more rest than would have been possible at home. The fact that they continued to do well after discharge from the hospital, while actively doing their housework and caring for their children, constituted one of the major advantages of cortisone treatment from their point of view.

The mechanism of action of cortisone in subacute thyroiditis is unknown. It is probably a nonspecific alteration of tissue response to inflammation, as in a variety of conditions. Cortisone inhibits the uptake of radioiodine by the thyroid gland and reduces the level of serum protein-bound iodine, but produces no evidence of hypothyroidism.[20] The urinary output of radioiodine is correspondingly increased.[21] Since the uptake of radioiodine in subacute thyroiditis is almost nil it is unlikely that cortisone influences the disease by reducing iodine uptake.

Summary

The effect of cortisone in 3 cases of subacute thyroiditis is described and 15 similar cases in the literature are briefly reviewed. All patients had a prompt subsidence of symptoms, usually within twenty-four hours of initiation of treatment, and a prompt recurrence when the drug was stopped too early. It is suggested that the effect is primarily suppressive, with excellent control of symptoms while the disease runs its usual self-limited course.

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SPECIAL ARTICLE

HOSPITAL SURVEY AND CONSTRUCTION PROGRAM IN MASSACHUSETTS*
A Five-Year Study

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BOSTON

DURING the year 1947 an unprecedented and far-reaching experiment in hospital administrative research was initiated in Massachusetts and throughout the country. Simultaneously throughout the 48 states, Alaska and the Territory of Hawaii, after a detailed inventory of existing facilities according to a predetermined plan, federal funds became available on a matching basis for hospital and health-center construction. For the first time in the history of the nation hospital building was to be undertaken according to one master plan; what may appear to be unbelievable was the certainty that under the provi-

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sions of the Hospital Survey and Construction Act (Public Law 725), the American voluntary hospital system was to maintain the independent position it had enjoyed since its inception.

To be sure, there were many who believed that socialized medicine and all the evils it represented would insidiously ensnare first the hospitals and finally the entire system of medical care. It will be recalled that early in the history of this program in Massachusetts the boards of trustees of at least two hospitals, in spite of the availability of federal funds, decided to proceed alone rather than risk the possibility of federal entanglements and ultimately the loss of control of their institutions. It was difficult to believe that acceptance of federal funds would not, in one way or another, subject the hospital to outside influence and restraining pressures.

Fortunately, these fears proved to be groundless; there were no federal controls. Hospitals aided under the program have maintained absolute freedom of action, and hospital trustees and staffs were completely won over. It must be confessed that, in most cases, this was not too arduous a task. With ever-increasing operating costs and mounting annual deficits, it had become more and more difficult for hospital trustees to set aside funds for improvements in physical plants. Often, in spite of successful fund-raising campaigns, building committees found that rising construction costs made it almost impossible to complete programs as originally planned without federal aid. In several institutions, as a result of the Act, trustees have been able to keep intact unrestricted endowment funds that otherwise would have been dissipated to complete construction projects.

It is to the credit of those who planned the program that its administration did not necessitate, in any way, departures from existing patterns in the existing system of medical care. Yet, within the framework of the law, considerable leeway was permitted in developing the program best suited for the needs of the several states.

Unfortunately research in the field of administrative medicine may too often become unrealistic and expensive. Large sums, for example, have been expended in the belief that home medical care, for certain segments of the population, should be provided by hospital-hired physicians, thereby reducing the number of inpatients. Such programs are extremely expensive to the hospital, and, as soon as outside funds supporting this type of research are withdrawn, the program will of necessity collapse. It is obviously impossible for the hospital budget to support a home-care program without continuing funds from some outside source.

Such lack of realism was excluded from the structure of the hospital survey and construction program. Under the provision of the law and its regulations it was not permitted to embark on experimental programs that would not make a definite and long-standing improvement in community facilities for medical care.

Developing the State Plan

The first state plan for the administration of Public Law 725, which was published in 1947,[1] was subsequently revised to take into account obsolescent and substandard facilities. A certain proportion of the general hospital buildings in the State had been constructed at the turn of the century and was considered obsolescent, according to modern standards. Some buildings were of frame construction or substandard in other respects.

Subsequent revisions of the plan gave heed not only to obsolescence but also to the adequacy of the major departments in hospitals. Consideration was given to such items as the surgical department, the maternity department, laboratories, x-ray facilities, kitchens, dining rooms, power plants, laundries and patients' service facilities, including elevators, diet kitchens and utility rooms. By this method the hospital's priority in the state plan not only reflected its bed count, type and age of structure but also afforded a complete evaluation of its patient and service facilities. This feature was unique in the Massachusetts plan.

In addition to the priority scheme established for general hospitals special consideration was given in the Massachusetts plan to certain other categories. It was found, early in the program, that a large proportion of the federal funds allotted to Massachusetts would be, of necessity, allocated to rural areas or to urban centers removed from Boston, where the teaching hospitals closely allied to the State's three medical schools are located. It was believed that the training program of these teaching hospitals was vital to the proper staffing of the steadily growing hospitals in the more peripheral areas of the State. For this reason teaching hospitals, closely associated with medical schools and providing, in addition, facilities for postgraduate study of interns, residents and graduates, were declared eligible for federal assistance.

Furthermore, it became evident in 1947 that obstetric departments in many general hospitals and some maternity hospitals were inadequate from many points of view. It will be recalled that, during 1946 and 1947, extreme overcrowding on maternity wards was associated with extensive outbreaks of epidemic diarrhea of the newborn, not only in Massachusetts but in many other states.[2,3] The hospital survey revealed, among other things, such inadequacies as non-segregation of delivery suites and maternity wards, lack of sufficient labor rooms and overcrowding in newborn nurseries. This calls to mind a nursery in one hospital, located on the top story of a nonfire-resistant building, with bassinets for 60 newborn infants in one large area. Fortunately, this hospital is no longer in existence. Because of these conditions, it was believed that alterations and improvements of such poor facilities should be encouraged with federal assistance.

A special priority was therefore established whereby general hospitals, not otherwise holding a high priority and requiring essential improvements in the maternity departments, were declared eligible for participation in the hospital survey and construction program.

The survey of existing facilities revealed yet another problem. In several sections of the State it was found that frame dwellings had been converted into small general hospitals. Some of these buildings were overcrowded and inadequate in patient and medical service facilities and constituted real fire hazards. Fortunately, many of these buildings were located in hospital service areas that were subsequently found to hold high priority for federal assistance.

In Massachusetts the administration of the program has been a joint endeavor of the Massachusetts Department of Public Health and its hospital advisory committee; this committee, which is required by law, was appointed by the Governor.

The Construction Program

Funds have been distributed for hospital and health-center construction since 1948, with a total allocation to Massachusetts of $13,990,190. Except for the fiscal year beginning July 1, 1953, when the annual appropriation was reduced to $65,000,000, at least $75,000,000 had been allocated annually throughout the country. In 1950 the appropriation had been doubled by an amendment to the law to $150,000,000 annually. However, with the advent of the war in Korea, the appropriation was again reduced to the original figure of $75,000,000. In Massachusetts, because of the large number of applications for federal funds, individual construction projects have been limited to a grant of $250,000.

As originally anticipated the program in Massachusetts was limited to the building of general hospitals, hospitals for chronic disease and public-health centers. The survey of existing facilities indicated that, on a state-wide basis, there were sufficient tuberculosis beds. Furthermore, it was found that replacement of outmoded facilities and overcrowding in mental hospitals constituted problems that were too great to be handled with the limited funds available under this program.

A total of 58 construction projects has been approved thus far for federal funds. Geographically, these projects are distributed from Newburyport and Methuen to Hyannis on Cape Cod and from Boston to North Adams in the Berkshires. New hospitals have been built or approved in Needham, Athol, Milton, Clinton, Palmer, Lynn (Lynn Union Hospital), Groton, Springfield (Wesson Maternity Hospital) and Webster. Projects for the purchase of equipment only have been approved for three additional new hospitals (Bon Secours Hospital, Methuen; St. Vincent's Hospital, Worcester; and the Carney Hospital, Boston).

Several of these hospitals, in operation for only two or three years, have shown excellent occupancy rates. The hospital in Athol (the only new hospital in the program that did not replace an existing facility) had an occupancy rate of almost 80 per cent during 1952. The Wing Memorial Hospital, Palmer, with a rate approximately 70 per cent after a year, and the Milton Hospital, with an occupancy rate of 77 per cent in 1952, indicate that the new hospitals are filling a real community need.

In the 58 projects receiving federal aid from 1948 to 1953, 3671 beds and 602 bassinets were added (Table 1). It must be borne in mind, however, that in several extensive building programs, such as that of the Beth Israel Hospital, federal participation was limited to the purchase of new equipment.

General Hospitals

Of the 45 general hospitals receiving aid 8 were teaching hospitals. Two special maternity hospitals were granted funds. Of the latter, one project, the Wesson Maternity Hospital, was completely new, and the second was a maternity section for the Martha's Vineyard Hospital.

Teaching Hospitals

Funds were made available to the majority of the teaching-hospital projects primarily for the purchase of equipment. A few were construction projects. At the Massachusetts Eye and Ear Infirmary operating rooms and 22 beds were added. A project at the Peter Bent Brigham Hospital gave 39 additional beds and expanded outpatient-department facilities. At the Boston Lying-in Hospital several clinics were added in the outpatient department, and at the New England Center Hospital the construction of a new pathology department was started with federal funds. At the Boston City Hospital a new center for premature infants is being planned. It is expected that this unit will make a real contribution to child health in the city.

Chronic-Disease Hospitals

Only 9 projects were approved for chronic-disease hospitals. Notwithstanding the obvious lack of beds revealed in the survey, there has not been considerable interest in the construction of chronic-disease facilities. The Municipal Hospital, currently being completed in Springfield, is the largest chronic-disease hospital to be constructed in Massachusetts with federal aid. The operation of such a facility, by a community the size of Springfield, constitutes a new departure in medical care. The progress of this hospital is being closely watched.

A new chronic-disease unit is being constructed in Holyoke, replacing a typical city infirmary. This institution will provide care not only to welfare recipients but also to private patients in Holyoke and in neighboring communities who require long-term

treatment. Large, multiple-bed wards will make it possible to erect a hospital of about 120 beds at a cost slightly in excess of $1,000,000. Whereas routine medical and nursing care will be provided within this hospital the facilities of nearby general hospitals will be available for patients who need more complicated skills. Emphasis in this institution will be placed on occupational therapy, physiotherapy and recreational activities.

TABLE 1. *Distribution of Projects by Type of Medical Facility.*

TYPE OF FACILITY	NO. OF HOSPITALS	NO. OF BEDS ADDED	NO. OF BASSINETS ADDED	BED CAPACITY ON COMPLETION	BASSINET CAPACITY ON COMPLETION
Maternity hospital	2	94	104	118	114
Teaching hospital	8	694	121	3794	594
Other general hospital	35	2119	377	4088	934
Totals	45	2907	602	8000	1642
Chronic-disease hospital	9	764		1835	
Public-health center	3				
Laboratory	1				
Grand Totals	58	3671	602	9835	1642

TABLE 2. *Distribution of Projects by Hospital Regions.*

REGION	BEDS ADDED	BASSINETS ADDED
Boston*	1987 (54.1%)	305 (50.7%)
Beverly-Salem	136 (3.7%)	50 (8.3%)
Barnstable	77 (2.1%)	—
Worcester	664 (18.1%)	67 (11.1%)
Springfield†	684 (18.6%)	156 (25.9%)
Pittsfield	123 (3.4%)	24 (4.0%)
Totals	3671	602

*Quincy and Brookline Health Centers.
†Amherst Health Center.

Public-Health Centers

It will be noted that, in spite of the dearth of public-health centers throughout the State, only 3 were approved, the first in Quincy, and the second in Brookline; the third is being planned in Amherst, which is under the jurisdiction of the University of Massachusetts. Although such construction holds a high priority in the state program there has been little interest in this category on the part of city and town officials.

If there had been more enthusiasm for the development of local health units in Massachusetts the demand for centers might have been greater. However, since there is no provision for either federal or state subsidy for the operation of local health units, this type of activity has been limited.

In other parts of the country the idea of the public-health center has been accepted more readily, possibly because of pressing health problems in these regions. Until there is a greater demand for centers on the part of the public and until the need for public-health centers in Massachusetts is more adequately defined, emphasis in the program will, of necessity, be centered on other categories. The relative scarcity of federal funds and the urgent demand for assistance on the part of hospital trustees necessitate this course of action for the present.

Geographic Distribution

Projects were built in all 6 regions of the State (Table 2). Of the 3671 beds added in all categories 1987, or 54 per cent, were in the Boston region, and projects in the Worcester and Springfield regions added 1348 beds (36.7 per cent). Among the general hospitals most beds were added in urban areas (intermediate), not including Boston, Worcester and Springfield (the base areas of the State). Of the total of 2907 general-hospital beds 355 (12 per cent) were built in rural areas (population less than 25,000).

Distribution by Hospital Service Area

Up to the present only 764 chronic-disease beds have been added (Table 3). Base-area projects accounted for 429, or 56 per cent, whereas 203 were in intermediate areas and 132 (17 per cent) in rural areas. Of the 9 chronic-disease projects, 6 were additions to general hospitals, 2 were new hospitals, and 1 was an addition to an existing building. Of the 9 projects 3 will provide long-term care, and the remainder will afford facilities for short-stay patients with chronic disease.

It is apparent that existing and newly planned chronic-disease hospitals, with a total of 3291 acceptable and 647 nonacceptable beds, provide care for only a small portion of the patients requiring either short-term or long-term care for chronic disease.[4] Nursing homes in Massachusetts presently make available 9781 beds for patients requiring long-term care.[5] It is obvious, therefore, that nursing-home facilities are urgently needed and deserve a considerable amount of attention from the licensing agency, which,

in Massachusetts, is the Division of Hospitals of the Department of Public Health.

Allocation of Funds

The allocation of federal funds by hospital region and type of facility merits careful study (Table 4). It will be seen that of the total funds allotted to Massachusetts ($13,990,000 since 1948) 79 per cent was allocated to general hospitals, including teaching hospitals, maternity hospitals and laboratories. Funds designated for chronic disease amounted to 17 per cent of the total money, whereas only $614,000 (4 per cent) was utilized for public-health centers.

It is interesting that the amounts utilized for chronic-disease units and public-health centers were sufficient to cover all completed applications. Although the greatest proportion of the Massachusetts allocation went to general hospitals, applications of this type exceeded by far the amount of available funds. Thus far in the program, applications have been accepted only from the two highest priority groups in the general-hospital category.

In a recent survey of general hospitals it was found that at least $12,000,000 in federal funds could be used, in the next few years, notwithstanding a limitation of $250,000 to any one grant.[5] Applications for assistance in the building of several fine teaching projects in Boston have been filed. Lack of funds has thus far made action on these applications impossible. It is hoped that future allocations will be made available for such projects.

When consideration is given to the geographic distribution of projects it is apparent that 60 per cent of the money was allocated to the Boston region (Boston proper and the Greater Boston area), 17 per cent to the Springfield, 13 per cent to the Worcester, 4 per cent to the Beverly–Salem, 3 per cent to the Barnstable and 1.8 per cent to the Pittsfield region. It is reassuring to note that, by and large, there is a fair degree of correlation between the percentage distribution of funds and the population density. It must be realized that the priority scheme for general hospitals, which is based on unmet bed needs,[1] might, in some cases, tend to lessen the degree of correlation. Table 5 indicates the amount and percentage of funds allocated to each base-area and to the remainder of the region. In the Boston region 16.2 per cent of the total funds went to Boston proper, and 44.6 per cent to the remainder of the region. For Worcester the figures were 4 per cent for the city itself and 9 per cent for the remainder of the region. In Springfield 3.6 per cent of the total allocation was allotted to the city, and 13.7 to the remainder of the region.

From these figures one may conclude that, as the general hospitals in the urban areas of the State are being improved and enlarged, marked deviation in patient flow from the base area to the surrounding communities may be the inevitable result. In the

TABLE 3. *Distribution by Hospital Service Area.*

TYPE OF AREA	GENERAL HOSPITAL		CHRONIC-DISEASE HOSPITAL	TOTALS	
	BEDS	BASSINETS	BEDS	BEDS	BASSINETS
Base	1248	237	429	1677	237
Intermediate*	1304	268	203	1507	268
Rural	355	97	132	487	97
Totals	2907	602	764	3671	602

*Also 3 health centers.

TABLE 4. *Distribution of Funds* by Type of Facility and Hospital Region.*

TYPE OF FACILITY	BOSTON REGION	BEVERLY–SALEM REGION	BARNSTABLE REGION	WORCESTER REGION	SPRINGFIELD REGION	PITTSFIELD REGION	TOTALS
	$	$	$	$	$	$	$
Teaching hospital	1,259,000						1,259,000
General hospital	5,273,000	564,000		1,814,000	1,423,000	250,000	9,324,000
Maternity hospital			60,000		250,000		310,000
Chronic-disease hospital	1,498,000		381,000		500,000		2,379,000
Public-health center	364,000				250,000		614,000
Laboratory	104,000						104,000
Totals	8,498,000 (60.8%)	564,000 (4.0%)	441,000 (3.1%)	1,814,000 (13.0%)	2,423,000 (17.3%)	250,000 (1.8%)	13,990,000

*Population breakdowns of hospital regions in Massachusetts (4,690,514 population) are as follows: Boston region, 3,106,000 (66.2 per cent); Beverly-Salem region, 387,000 (8.3 per cent); Barnstable region, 51,000 (1.1 per cent); Worcester region, 524,000 (11.2 per cent); Springfield region, 487,000 (10.4 per cent); and Pittsfield region, 134,000 (2.8 per cent).

Greater Boston area, for example, construction projects in Arlington, Concord, Malden, Medford, Milton, Natick, Needham and Norwood have increased the number of suburban beds, and, as local residents utilize community resources to a greater extent, decreased occupancy rates may result in some Boston hospitals. These figures emphasize the need of planning on a regional basis.

tage of the program. This is particularly true of rural areas, where 7 new hospitals have been built or are being erected.

Unfortunately, boards of trustees of several general hospitals have had to wait for two or even three years, all available funds having been allocated to hospitals with higher priorities. It is expected that future appropriations will make it possible to continue this

TABLE 5. *Distribution of Funds by Type of Facility and Hospital Region (Base Areas*).*

TYPE OF FACILITY	BOSTON REGION		WORCESTER REGION		SPRINGFIELD REGION	
	BOSTON PROPER $	LESS BOSTON $	WORCESTER PROPER $	LESS WORCESTER $	SPRINGFIELD PROPER $	LESS SPRINGFIELD $
Teaching hospital	1,259,000					
General hospital		5,273,000	556,000	1,258,000		1,423,000
Maternity hospital					250,000	
Chronic-disease hospital	901,000	597,000			250,000	250,000
Public-health center		364,000				250,000
Laboratory	104,000					
Totals	2,264,000 (16.2%)	6,234,000 (44.6%)	556,000 (4.0%)	1,258,000 (9.0%)	500,000 (3.6%)	1,923,000 (13.7%)

*Population breakdowns of base areas in Massachusetts (4,690,514 population) are as follows: Boston, 801,000 (17.1 per cent), and region less Boston, 2,305,000 (49.1 per cent); Worcester, 291,000 (6.2 per cent) and region less Worcester, 233,000 (5 per cent); and Springfield, 218,000 (4.7 per cent), and region less Springfield, 269,000 (5.7 per cent).

The percentage of funds by type of hospital service area is recorded in Table 6. Base areas, with 31.9 per cent of the population, received 23.7 per cent of the funds. Intermediate areas, with 60.6 per cent of the population, obtained 58.9 per cent of the funds, and rural areas, with 7.5 per cent of the population, were allocated 17.4 per cent. Although the last figure seems relatively large in comparison with the population

TABLE 6. *Distribution of Funds by Type of Hospital Service Area.*

TYPE OF AREA	POPULATION	FEDERAL FUNDS
Base	1,496,000 (31.9%)	$ 3,319,000 (23.7%)
Intermediate	2,842,000 (60.6%)	8,235,000 (58.9%)
Rural	352,000 (7.5%)	2,436,000 (17.4%)
Totals	4,690,000	$13,990,000

percentage it must be recalled that it was the original intent of the program to improve, first of all, facilities in rural areas. In the Massachusetts survey it was found that urban centers besides Boston, Springfield and Worcester had a marked deficit in general-hospital beds. It is for this reason that 58.9 per cent of the funds was allocated to these intermediate areas.

In the plan for administration of the law Massachusetts is divided into 71 hospital service areas, of which 3 are base (teaching areas), 43 intermediate (urban areas) and 25 rural areas. Of the 27 intermediate areas, 19 have had approved projects (70 per cent); of the 12 rural areas, 10 (83 per cent) have had approved projects. These figures indicate that high-priority areas have taken adequate advan-

program, which has been responsible for great improvements in the medical-care facilities of Massachusetts.

SUMMARY AND CONCLUSIONS

The operation of the Hospital Survey and Construction program in Massachusetts, as well as throughout the country, has demonstrated that voluntary hospitals may accept financial assistance without being subjected necessarily to governmental control. The program has been accorded general acceptance in Massachusetts, where state-wide planning and a continuing inventory of available hospital resources are making a real improvement in medical administrative practice.

In Massachusetts the greatest contribution to medical-care facilities has been in the general hospitals.

In accordance with the original intent of Congress rural areas have manifested the greatest degree of improvement in health facilities, and new hospitals have been erected or are being planned in 7 rural hospital service areas, replacing existing, substandard and, in some cases, hazardous structures.

Of $13,990,000 allotted to Massachusetts, $8,235,000 (58.9 per cent) has gone to hospitals in urban centers (besides Boston, Worcester and Springfield) where, as revealed by the survey, the need for additional hospital beds was most urgent.

To improve teaching and training in the fields of medicine and nursing boards of trustees of several teaching hospitals in Boston have accepted financial assistance under this program. It is hoped that additional aid for meritorious projects, which will broaden

the scope of teaching in Boston, will be forthcoming in the future.

A special program to improve medical care for mothers and newborn children in maternity hospitals and obstetric departments of general hospitals has been undertaken.

Planning on a state-wide basis for chronic disease is another aspect of the program. Of 9 chronic-disease projects completed or planned, 6 provide or will provide facilities for the short-stay chronically ill patient, and 3 will offer long-term care. A large chronic-disease hospital, municipally owned, is a noteworthy development in the field of geriatrics in Massachusetts. In another community a typical city infirmary is being replaced with a chronic-disease hospital.

Of 3 health centers approved for federal aid, only 1 has been completed. Although health centers hold a high priority in the Massachusetts plan there has been little activity in this regard. It is evident that a real appraisal of local health organizations is urgently needed before considerable expenditures are made for health centers.

As hospitals and medical-care facilities are being enlarged and improved in accordance with demonstrated need the program is making a vital contribution to the welfare of the citizens of the Commonwealth.

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MEDICAL PROGRESS

ACTH AND CORTISONE THERAPY OF RHEUMATIC FEVER AND RHEUMATIC CARDITIS*

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BOSTON

THE apparent usefulness of cortisone and ACTH in the treatment of acute rheumatic fever and rheumatic carditis was first pointed out by Hench and his associates[1] shortly after they had reported the remarkable suppressive effect of these hormones on rheumatoid arthritis.[2,3]

Since that time a number of investigators, expressing a variety of opinions, have presented articles dealing with this subject. Some[4-28] have confirmed Hench's findings, and, although most of these investigators believe that more work needs to be done before the therapeutic value of the hormones can be completely defined, they have interpreted their observations as either suggesting or as definitely indicating that the hormones, when properly used, are helpful in the treatment of acute rheumatic fever. Others[29-42] have been more conservative in their conclusions, and, although they also believe that further studies are indicated, they have not been willing to express any definite opinion about the effectiveness of hormone therapy. Finally, there are those[43-52] who do not believe that ACTH or cortisone has any great advantage over other methods in the treatment of rheumatic fever and rheumatic carditis.

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The lack of unanimity of opinion and the variety of points of view that have been expressed can be appreciated by a consideration of the following citations and quotations selected from some representative articles:

Massell, Warren and Sturgis[5] noted that with hormone therapy there was a striking suppression of many of the manifestations of rheumatic fever, including those of carditis, and concluded that there was "considerable promise that this therapy when given early in an attack of rheumatic fever may, at least in some instances, prevent heart damage."

Wilson and her associates,[16] who treated patients with moderately large doses of ACTH for about a week only, interpreted their observations as indicating that this therapy "is followed by arrest and termination of active carditis without overt clinical evidence of residual cardiac damage." They believed that "the natural course of active carditis was favorably altered by decreasing both the severity and the duration of the attack."

Hench,[3] Barnes et al.[4] and their associates likened the role of ACTH and cortisone to that of "firemen whose function it is to put out a fire in its incipiency." They presented data strongly suggesting that these hormones are capable of blocking the exudative phase of rheumatic fever, and they stated that their "results to date give us considerable reason to hope that early and adequate administration of

cortisone or corticotropin in initial and recurring attacks of rheumatic fever and continuation of their administration until the disease has finished its active course will forestall permanent cardiac injury in the great majority of cases."

In a study of ACTH treatment of 18 children early in their initial, acute attacks of rheumatic fever, Kelley[20] noted that after therapy had been discontinued "none of these patients had evidence of cardiac enlargement, abnormal electrocardiogram, or other evidence of active carditis." Although he considered his series of observations to be inadequate to answer the question of whether early initiation of hormone therapy "in adequate daily dosage and continuation of such therapy for an adequate period of time will prevent or ameliorate the patient's eventual cardiac residual damage resultant from an attack of rheumatic fever," he interpreted the low incidence of residual cardiac damage as being encouraging, and he believed that the results indicated "that this approach to the problem should be more extensively pursued and evaluated."

The importance of early hormone treatment with "adequate intensive dosage" was also emphasized by Kroop et al.,[24,25] who observed that such treatment seemed "to result in the prevention of valvulitis as evidenced by the subsequent absence of murmurs, and no increase in heart size." These investigators also found the suppressive effect of cortisone on severe carditis to be "life saving."

Like Kelley and Kroop, Greenman and his associates[28] were greatly impressed by the results of early intensive therapy of initial attacks of rheumatic fever. They interpreted their data as indicating that "cortisone in adequate amounts under the regimen employed may prevent cardiac abnormalities in patients without previous heart damage when given within six, and especially within two, weeks of onset." Although "cardiac residua of previous attacks do not disappear" they considered that "acute second and subsequent attacks, or chronic active disease" could be beneficially influenced.

Dorfman and his co-workers[30] noted a marked suppressive effect of ACTH on the manifestations of active rheumatic fever, including those of carditis. However, they believed that there was "as yet no conclusive evidence . . . whether ACTH therapy affects the natural course of rheumatic fever," that, as used in their studies, "ACTH therapy did not uniformly prevent death due to acute rheumatic pancarditis" and that there was "no evidence to indicate whether treatment of active rheumatic fever with ACTH changes the incidence of late valvular deformities."

Kuttner et al.,[35] in one article, observed "definite improvement in the general condition of all patients" treated with cortisone or ACTH but did not believe that there was any clear evidence whether the use of these hormones "significantly decreased the duration of active carditis or influenced cardiac damage." In a later article they[36] again emphasized the point that "at the present state of knowledge it is not known whether the administration of adrenal cortical hormones results in the prevention or even significant diminution of damage to cardiac structures."

Definite benefit from the hormones was obtained by Young and Rodstein[38] in severely ill rheumatic children, especially those with congestive heart failure. At the same time, after observing the appearance of "new significant murmurs" in a number of patients with chronic active disease, they expressed the opinion that this observation tended to "cast doubt on the optimism voiced particularly by Massell and by Wilson concerning the potential value of these drugs in preventing cardiac damage."

Bywaters and Dixon[40] considered the action of ACTH, although "similar to that of salicylates," to be "somewhat more powerful." Nevertheless, they found no evidence "to prove or disprove the view that either remedy, hormone or salicylate, affects incidence of cardiac residua, decreases mortality, or decreases the period of invalidity."

The results of cortisone treatment of 12 children with rheumatic carditis were found by Chamberlain, Hay and Freeman[43] to be "disappointing." Boone and Beach,[44] similarly, were not impressed by hormone therapy and were "unable to demonstrate that it was clearly of benefit" in any of 6 severely ill patients whom they treated.

Johnson and Ferencz[47] compared the incidence of rheumatic heart disease in 100 children treated with ACTH or cortisone with that in 80 patients observed before the use of hormone therapy. They failed to find any significant difference in the figures for the two groups.

The effect of cortisone, ACTH and salicylate were compared by Rowe, McKelvey and Keith[50] in a series of 41 patients with rheumatic fever. After calling attention to the fact that the benefits of salicylates are limited these authors pointed out that their study failed to show "any significant difference between hormones and salicylates as far as one can measure the effects on the heart" and thus implied that the benefits of hormone therapy are also limited. In fact they concluded that salicylates are "the more practical agent in the treatment of the general case of rheumatic fever. . . . "

A preliminary report of a co-operative study conducted in 13 research centers in the United States, Great Britain and Canada under the sponsorship of the American Heart Association's Council on Rheumatic Fever and the British Medical Research Council indicated that there was "no consistent pattern" in the response of the various manifestations of rheumatic fever in patients treated with

ACTH, cortisone or aspirin and that "no firm conclusions" could be drawn "concerning the drug most effective in the control of the acute illness." This report, which was presented before the American Rheumatism Association in Chicago in June, 1952,[51] and again before the Eighth International Congress of Rheumatic Diseases in Geneva, Switzerland, in August, 1953,[52] has been published or referred to in editorials in many scientific journals in this country and abroad and as a result has had considerable influence on medical opinion throughout the world.

It is evident from the reports cited that a number of divergent opinions regarding the usefulness of hormone therapy in rheumatic fever and rheumatic carditis are held by investigators who have worked on the problem, and for the physician confronted with these many different opinions the status of cortisone and ACTH therapy certainly must be confusing. This review, therefore, is an attempt to determine from the observations reported in the medical literature what definite effects the hormones have in rheumatic fever and to determine from these effects what value the hormones may have in the treatment of patients with this disease.

In the collection of information an effort has been made to cover all relevant articles published in the English language between April, 1949, and January, 1954, but some studies may have been inadvertently overlooked.

It is beyond the scope of this review to include a comparison of the effects of ACTH and cortisone with those of salicylates and other antirheumatic drugs.

There are three possible ways in which therapeutic agents might be of value in the treatment of rheumatic fever. The first is by shortening the duration of the disease. The second is by reducing the severity of the attack and thereby saving lives in the kind of attacks of rheumatic fever that ordinarily would be fatal. The third is by preventing heart damage or reducing the amount of heart damage that results from rheumatic fever.

In the evaluation of data bearing on the problem of the therapeutic value of cortisone and ACTH, each of these three possible ways by which the hormones may influence the outcome of rheumatic fever is considered.

Any effectiveness for reducing the severity of the attack and for preventing heart damage would be dependent on the ability of the drugs to suppress the rheumatic inflammatory process, particularly that which involves the heart. Therefore, consideration is first given to data indicating the degree to which the hormones can suppress rheumatic inflammation.

To facilitate a discussion of these aspects of the problem the remainder of this review is divided into the following five sections: the suppressive effect of the hormones on the rheumatic inflammatory process; the effect of hormone therapy on the duration of the rheumatic attack; the life-saving effect of hormone therapy; the effectiveness of hormone therapy in the prevention and reduction of heart damage; and a summary and discussion.

Suppressive Effect on the Inflammatory Process

Evidence regarding the possible suppressive effect of cortisone and ACTH on the inflammatory process of rheumatic fever is available from reports of clinical observations of the responses of the various manifestations of rheumatic fever to hormone therapy and, to a more limited extent, from a relatively few published observations on the microscopical appearance of tissues obtained by biopsy or at autopsy of hormone-treated patients.

Response of Manifestations of Rheumatic Fever

The important clinical and laboratory manifestations of rheumatic fever may be divided into two groups: the extracardiac manifestations, including arthritis, fever, subcutaneous nodules, erythema marginatum, chorea, and elevation of the erythrocyte sedimentation rate; and the manifestations of active carditis, including tachycardia, gallop rhythm, pericarditis, prolongation of the PR interval in the electrocardiogram and congestive heart failure. Reported observations on or published opinions regarding the effect of ACTH and cortisone on each of these manifestations is considered.

Polyarthritis and fever. The response of polyarthritis and fever to cortisone and ACTH is about the only effect of hormone therapy concerning which there is practically complete agreement among investigators. Almost without exception the physicians who have reported their experience have noted that these two manifestations of rheumatic fever were brought under control rapidly by such treatment, so that in the vast majority of cases they subsided completely within one to three days. Rarely, four to seven days were required for all traces of fever and arthritis to disappear.

Subcutaneous nodules. The apparent suppressive effect of the adrenocortical hormones on the subcutaneous nodules of rheumatic fever was first observed by Massell and his associates[5,6,8] at the House of the Good Samaritan. These early studies included 5 patients with nodules who were treated with ACTH. In 4 patients the nodules disappeared within periods varying from fourteen to fifty days after the beginning of therapy. In the fifth patient, who received very small amounts of hormone (average of 14.2 mg. of a lyophilized preparation a day), the nodules gradually diminished in size during forty days of treatment and did not disappear completely until three weeks after termination of therapy.

In a later study at the House of the Good Samaritan[10] the clinical course of nodules in 3 of the previ-

ously reported cases and in 11 additional ones (total of 14 patients) treated with cortisone or ACTH was compared with the course in 46 patients not treated with hormones. This particular study included only patients with few or multiple nodules, those with one or two nodules being excluded. The nodules in all the patients who received hormones became detectably smaller within one or two weeks and completely disappeared within two to eight weeks of the beginning of therapy. In no case were new nodules observed during treatment.

The clinical course of the nodules in these patients contrasts strikingly with that of the patients who did not receive hormone therapy. In the latter group change in size of nodules usually occurred very slowly; in most cases the nodules could be readily detected for a number of months, and in only 17 per cent did the nodules disappear within eight weeks. It is of further interest that many of the patients who were not treated with hormones received salicylate therapy for varying periods and that new nodules were frequently observed to appear while salicylates were being administered.

In addition to the cases reported by Massell et al. the medical literature contains a variable amount of information regarding 14 other cases treated with cortisone or ACTH.

Wilson and her associates[15,16] noted the presence of nodules in 2 patients in their series of ACTH-treated cases. In 1 of these the nodules were first observed five days after the end of a one-week course of treatment, and they continued to be present for an additional three weeks even though the patient was given a second course of ACTH for four days. The other patient was first observed to have nodules some time after the completion of seven days of treatment. It is to be noted that in both cases the duration of hormone therapy was relatively short and that the nodules appeared during periods when hormones were not being administered.

Nodules were present in 3 of 22 ACTH-treated cases reported by Dorfman and his co-workers.[30] These physicians observed that "the nodules disappeared in all patients during the course of therapy" and "in none of these cases did they reappear subsequent to the withdrawal of therapy."

Investigators at New York University — Bellevue Medical Center noted nodules in a total of 5 patients treated with ACTH or cortisone. Details regarding 3 of these patients were presented by Kuttner et al.[35] In 1 patient with multiple nodules who was given hormone therapy for a total of forty-nine days the lesions were observed to have decreased in size and number within ten days, but a few nodules persisted for six weeks. Nodules also disappeared in the second patient during hormone treatment, but the authors believed that the nodules had already almost disappeared before therapy was begun. In the third patient numerous nodules disappeared by the end of ten days of therapy, but in this case also the nodules had already been decreasing in size and number before the beginning of treatment. The disappearance of nodules during hormone therapy in 2 additional patients at the Bellevue Medical Center is mentioned in another report by Bunim and his associates,[36] who pointed out that new nodules did not appear in any patient receiving hormone therapy. Although these authors stated that in some cases nodules "seemed to resolve sooner than would otherwise be expected" Kuttner et al.[35] expressed the opinion that it was "impossible to be sure that the nodules might not have disappeared in the same length of time without hormone therapy."

Bach, Freedman and Bernstock[21] observed rheumatic nodules in 2 of 4 patients treated with cortisone. One patient, who was first treated with salicylates and then with about 100 mg. of cortisone a day, had nodules when the cortisone dosage was reduced to 75 mg. per day. The "dosage was restored," and "cortisone was finally discontinued after fourteen weeks." By this time the nodules, which had been slowly decreasing in size, were no longer visible. The second patient manifested widespread rheumatic nodules while being treated with fairly large doses of sodium salicylate (6 to 12 gm. a day). When treatment was changed to cortisone the nodules rapidly decreased in size, and after two weeks of treatment they could not be definitely discerned except over the left elbow, from which they finally disappeared about seven or eight weeks after the beginning of therapy.

Griffith and his associates[22,23] reported that subcutaneous nodules were present in 1 of 12 patients treated with ACTH. In this patient the nodules "diminished in 72 hours and could not be found after 1 week of therapy."

Fischel, Frank and Ragan[53] described a patient with "crops of subcutaneous nodules" that persisted during a period of four weeks without medication and then during an additional eleven-day period of treatment with "small doses of aspirin." When treatment was changed to ACTH, the nodules regressed, but hormone therapy was continued for only two weeks. After treatment had been discontinued there was a mild recurrence of rheumatic fever whose manifestations included the transient appearance of a nodule on one thumb.

In addition to the reports just reviewed there are two that touch briefly on the possible effect of cortisone and ACTH on nodules. One of these is a paper by Bywaters and Dixon[40] in which it is stated that a fresh nodule appeared in a patient during treatment with ACTH. The authors did not elaborate on the case, but it can be assumed that very small amounts of the hormone were used since most of the other cases discussed in the same paper were treated with only 50 mg. of ACTH a day for a total of only eight days.

The other paper is by Rowe, McKelvey and Keith,[50]

who reported their experience with 41 patients with rheumatic fever. Fifteen of these were treated with cortisone, 13 with ACTH, and 13 with aspirin. The authors stated that "a small number of patients showed nodules at the start of treatment" and that "in the 3 treatment groups there were some instances of increases in numbers of nodules under therapy."

From the foregoing paragraphs it is evident that, exclusive of the scanty information furnished by the last two groups of investigators, data of varying completeness are available for a total of 30 patients with nodules treated with either cortisone or ACTH. It is also evident that new nodules did not occur during hormone therapy in any of these 30 patients except in 1 who was treated with relatively small amounts of cortisone (and in this case only when the daily dose was reduced to 75 mg.), that nodules reappeared or appeared for the first time after discontinuation of hormone therapy in a few patients who had been treated either with small doses or for a short period and that in most cases nodules either became definitely smaller or disappeared entirely during hormone therapy.

Although further observations on a larger series of cases will be necessary before final conclusions are justified the data reviewed above strongly suggest that the process that causes rheumatic nodules is suppressed by cortisone and ACTH.

Erythema marginatum. This rash is an interesting manifestation of rheumatic fever, but its significance as a sign of rheumatic activity is not fully understood. If the rash occurs during a period when other obvious signs of active rheumatic fever are also present it is frequently transient, or it appears intermittently. In some patients, after all other signs of active rheumatic fever (including such laboratory evidence as elevation of the sedimentation rate) have disappeared, the rash may continue to appear off and on for months or even years.

Data regarding the effect of cortisone and ACTH on erythema marginatum are still very limited. Wilson and Helper,[15] who referred to the rash as erythema multiforme, said that it disappeared within twenty-four to seventy-two hours in patients treated with ACTH, but the number of patients in whom this effect was observed and other details of their cases were not reported.

Bunim and his co-workers[36] noted that erythema marginatum cleared on the ninth day of therapy in a patient treated with cortisone and in another patient treated with ACTH.

Rheumatic skin rashes occurred in the period immediately preceding ACTH therapy in 4 patients of the series reported by Dorfman et al.[30] In 3 of these patients the rashes disappeared and did not reappear during the course of treatment. One patient, however, had "typical erythema marginatum" while receiving the hormone.

Bywaters and Dixon[40] noted no apparent influence of hormone therapy on the rash in 2 patients with rheumatic fever, but these patients were treated with only 50 mg. of lyophilized ACTH a day and for a total period of only eight days.

Sheinkopf and his associates[22] observed that in 1 of their patients treated with ACTH erythema marginatum disappeared within twelve hours, but during the first two weeks of therapy "the lesion could be caused to reappear if one of the 12-hour doses was omitted."

Two other groups of investigators,[24,50] without presenting any details regarding their experience, have stated that erythema marginatum occurred during treatment with cortisone or ACTH.

From this meager information gathered from the medical literature it is evident that the effect of hormone therapy on erythema marginatum cannot be ascertained.

Chorea. Although there is evidence that chorea is of rheumatic origin its significance as a sign of rheumatic activity is not fully understood. In this respect it is similar to erythema marginatum. In many cases chorea occurs in patients who have had other definite stigmas of rheumatic fever, but in these cases it usually appears at a time when other signs of rheumatic fever seem to be subsiding. In fact it is not unusual for chorea to develop even after the sedimentation rate has returned to within normal limits. In other cases chorea develops in patients who do not present and who have not previously had any other manifestations of rheumatic fever or rheumatic heart disease. These are cases of so-called "pure" chorea.

In the preparation of this review reports of 12 groups of investigators[8,24,33,41,46,49,50,54-59,61] were encountered that furnished a variable amount of information regarding the effect of cortisone or ACTH therapy in 38 cases of chorea. In 4 cases the authors indicated, without having given any specific data, that there was no improvement; however, in 3 observations were continued for a period of only ten to fourteen days. In 8 other cases the patients were considered to have shown definite improvement, or the chorea was said to have subsided quickly; however, detailed information regarding the duration of involuntary movements in these cases was likewise not given.

Of the remaining 26 cases the chorea was considered to have subsided within one or two weeks in 10, three or four weeks in 8, five or six weeks in 5, seven or eight weeks in 1 and more than eight weeks in 2. Thus, in the 26 cases for which data regarding duration of chorea are available, 18 patients, or 69 per cent, recovered within four weeks of the beginning of hormone treatment.

This figure compares favorably with the four-week recovery rate of only 22 per cent reported by Sutton and Dodge[62] in 150 cases of chorea observed at Bellevue Hospital in the days before cortisone and ACTH were available. The duration of chorea in the cases

described by Sutton and Dodge was measured from the time of admission to the hospital, and the figure cited is for all their cases combined (mild, moderate and severe).

The difference between the four-week recovery rate of 67 per cent for the hormone-treated cases and that of 22 per cent for the patients of Sutton and Dodge who did not receive any special form of therapy is impressive. It would be rash to come to any final conclusions regarding the efficacy of cortisone and ACTH in chorea on the basis of these figures alone — especially since the number of hormone-treated cases was relatively small and since there is no way of knowing whether the two groups of cases were comparable in severity and duration of chorea before therapy (in the hormone-treated cases) or to their admission to the hospital (in the cases not treated with hormones reported by Sutton and Dodge).

On the other hand the data are sufficiently suggestive to warrant consideration of the possibility that ACTH and cortisone actually suppress chorea and to indicate the need for further investigation of this effect of the hormones.

Elevated sedimentation rate. From the various articles reviewed data regarding changes in the erythrocyte sedimentation rate have been collected for over 100 patients treated with either cortisone or ACTH. In almost all cases an elevated sedimentation rate was reduced during therapy. A normal level was reached within two weeks in slightly over 50 per cent of cases and within three weeks in over 75 per cent. In relatively few did the sedimentation rate fail to become normal before the end of the treatment period.

Although the various ways in which different investigators have presented their data have made it impossible to compare the different reports in any exact fashion the impression gained from a review of these reports is that the speed and completeness with which an elevated sedimentation rate was affected was related to some extent to the severity of the illness but to a much greater extent to the dose of the hormones. Patients in whom there seemed to be little effect were usually treated with small daily amounts of the hormones or were treated for only a relatively short time.

It is generally agreed that the elevated sedimentation rate, which is usually present in active rheumatic fever, is secondary to the rheumatic inflammatory process. Most investigators also agree that treatment of rheumatic fever with cortisone or ACTH is very effective in lowering the sedimentation rate. However, there is no unanimity of opinion regarding the significance of the hormonal effect. Some interpret the decrease in sedimentation rate as reflecting a suppression of the rheumatic inflammatory process by the hormones; others express the opinion that the hormones directly influence the sedimentation rate and that, therefore, the course of the sedimentation rate cannot be used as a measure of what is happening to the rheumatic inflammatory process. Impetus to the second point of view has been furnished particularly by the observations of three groups of investigators.

Fearnley and Bunim,[63] in one communication, noted a close parallel between the fall in sedimentation rate and the fall in fibrinogen concentration. In a second article[64] they reported that a single injection of ACTH caused changes in plasma fibrinogen and serum protein levels of 7 normal persons. As a result of these observations they concluded that the fall in erythrocyte sedimentation rate after the administration of ACTH or cortisone "is the result of a direct effect of these hormones on certain chemical constituents of the blood and should not be interpreted as an indication of clinical improvement."

Vaughan, Bayles and Favour,[65] in a study of patients with rheumatoid arthritis and scleroderma, also observed that the decrease in sedimentation rate was related to a depression of the gamma-globulin and fibrinogen levels in the blood by these hormones, and they concluded that "at the present state of our knowledge the sedimentation rate cannot be used as an index of the effectiveness of hormone therapy on the active disease process."

Shock[66] reported that his associates had observed a "reduction in the sedimentation rate to subnormal values in 3 subjects without clinical evidence of disease who had initially normal sedimentation rates and in one subject who had an unexplained rapid sedimentation rate but in whom no other evidence of active disease could be found." Therefore, they concluded that the reduction in sedimentation rate that follows the administration of ACTH "is a manifestation of increased adrenocortical activity and is not exclusively dependent on its action on disease processes."

On the other hand, Fletcher, Dauphinee and Ogryzlo,[67] who made an extensive study of plasma proteins and the sedimentation rate in patients with rheumatoid arthritis, interpreted their findings somewhat differently. They confirmed the observations of others regarding the close correlation between the sedimentation rate and the concentration of plasma fibrinogen; they found that this correlation existed in rheumatoid arthritis patients before, during and after treatment with ACTH and cortisone. In the patients who responded well to hormone treatment but who then relapsed when therapy was discontinued the level of the fibrinogen followed fairly well the clinical course of the remission and the relapse. In exceptional cases, in which there was a poor clinical response, there was only a partial fall in the blood fibrinogen. From these observations they concluded that the sedimentation rate is a fair index of the level of the plasma fibrinogen and that the elevated fibrinogen content of the blood in turn appears to be an expression of the intensity of the pathologic process. It was their opinion that any direct effect on the fibrinogen level was probably minor.

A correlation of the sedimentation rate with clini-

cal signs of disease activity comparable to that observed by Fletcher et al. in rheumatoid arthritis has also been noted in rheumatic fever.[68] Hormone therapy is sometimes followed by a recurrence of fever and other clinical signs of active rheumatic fever when the course of treatment is completed. Fortunately, in many cases, especially when treatment has been given for at least a number of weeks, these rebounds are transient and again subside spontaneously. In these cases the sedimentation rate, having become normal during treatment, again becomes very high during the rebound and then gradually returns to normal once more after the subsidence of the clinical manifestations of the rebound. Sometimes termination of hormone therapy is not followed by the reappearance of clinical signs of rheumatic activity, and in these cases the sedimentation rate either continues to remain within normal limits or rises transiently to a level that, as a rule, is lower than the level accompanying clinical rebounds. This behavior of the sedimentation rate in rheumatic fever suggests that it reflects disease activity.

During treatment of rheumatic fever with cortisone or ACTH the sedimentation rate not only reaches normal limits but sometimes even falls to levels below those generally observed in healthy persons. On the basis of such cases of subnormal sedimentation rates Dorfman et al.[30] considered the possibility that the hormones had some nonspecific effect, but they pointed out that the sedimentation rate might parallel remission and thus indicate the effects of the hormones on rheumatic fever.

The tendency of some investigators to minimize the significance of the normal sedimentation rate that develops during therapy of rheumatic fever has been particularly criticized by Fischel, Frank and Ragan.[53] In referring to reports that ACTH, cortisone and salicylate may inhibit fibrinogen or globulin production and, per se, influence the sedimentation rate, they emphasized the fact that "the stimulus for the augmented fibrinogen and globulin production, the inflammatory process itself, is also suppressed" and that "this suppression may be of benefit."

It is apparent that, from the data reviewed here and the opinions expressed by various investigators, it is not possible to come to any final conclusions regarding the significance of the effect of cortisone and ACTH on the sedimentation rate in patients with rheumatic fever. However, the weight of evidence seems to support the view that, even though the hormones may have some direct depressing effect on the plasma proteins responsible for the sedimentation rate, the major effect on the sedimentation rate is dependent on suppression of the rheumatic inflammatory process.

Tachycardia and gallop rhythm. The subsidence of tachycardia in a number of patients during treatment with cortisone or ACTH has been reported by Massell and Warren,[8] Dorfman et al.,[30] Chamberlain, Hay and Freeman,[43] Shopfner and Seife[45] and Scheinkopf and his associates.[22,23] A similar effect was observed in some of the cases presented by Kuttner and her co-workers,[35] Brochner-Mortensen,[13] Young and Rodstein[38] and Bywaters and Dixon,[40] but in other cases reported by the same authors tachycardia persisted during therapy. Barnes et al.[4] noted that in most of their patients without carditis increased heart rates returned to normal in an average of only five and three-tenths days, but that in 3 patients with rheumatic carditis the rapid heart rates "returned to normal more slowly, if at all."

Relatively few observations on gallop rhythm during hormone therapy are recorded in the medical literature,[11,22,35,38] but from these observations there is a slight suggestion that the response of gallop rhythm is more consistent than that of tachycardia. In all but 2 of 14 reported cases of gallop rhythm the manifestation subsided within seven to ten days of hormone treatment.

Since tachycardia and gallop rhythm are often signs of active rheumatic carditis their disappearance in certain patients treated with cortisone or ACTH might be interpreted as evidence of a favorable effect on carditis, whereas the failure of these manifestations to respond to hormone therapy in other patients might be interpreted as an indication that carditis was not appreciably influenced. However, the situation is not quite so simple because factors in addition to carditis may be responsible for the presence of tachycardia and gallop rhythm.

Thus, although tachycardia may be due to active carditis it may also be secondary to permanent cardiac damage resulting from long-standing rheumatic fever or to fever even in the absence of carditis. Gallop rhythm can be caused by either active carditis or permanent myocardial damage and is usually also dependent on the presence of tachycardia.

In a patient with active carditis and fever the disappearance of tachycardia during hormone therapy could be due to a suppression of the carditis, but it also could be merely an indirect effect from the lowering of the temperature by the hormones. If such a patient had gallop rhythm in addition to tachycardia before therapy, the disappearance of the former manifestation might reflect a favorable effect of the treatment on the myocardium, but it also might be due simply to the reduction in heart rate.

On the contrary failure of tachycardia or gallop rhythm to subside during hormone therapy does not necessarily indicate a lack of suppressive effect of the hormone on carditis because permanent myocardial changes might be the more important cause of either or both of these manifestations, and such permanent changes could not be expected to be influenced by hormone therapy.

From these considerations it is evident that the problem of interpreting the response of tachycardia and gallop rhythm to treatment with ACTH or corti-

sone is by no means easy. In the absence of complete information regarding the relation of changes observed to other findings indicative of carditis, duration of rheumatic fever and carditis, changes in temperature, dosage of hormones given and duration of therapy the problem is especially complex. Since much of this information is lacking for the cases reported in the medical literature, it is concluded that the available data on tachycardia and gallop rhythm are not especially helpful in the evaluation of the suppressive effect of cortisone and ACTH on rheumatic carditis.

(To be continued)

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MEDICAL INTELLIGENCE

ANNULAR PANCREAS PRODUCING DUODENAL OBSTRUCTION IN INFANCY*

Report of a Successfully Treated Case

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ANNULAR pancreas is a rare congenital anomaly in which the second portion of the duodenum is encircled by a band of pancreatic tissue, leading to symptoms of high intestinal obstruction. The severity of the associated symptoms and findings varies with the grade of constriction. The many reports of the occurrence of this malformation as an incidental autopsy finding indicate its existence with little or no duodenal obstruction, and there are cases in which it has been demonstrated on surgical exploration for long-standing gastrointestinal complaints in adults. Furthermore, there are many cases, such as the one reported below, that are manifest in the newborn with symptoms so severe that early surgical relief is necessary if the infant is to survive.

Many explanations have been suggested for the mechanism of development of annular pancreas. The most generally accepted is that advanced by Lecco in 1910 and cited by McNaught,[1] Lehman,[2] Gross and Chisholm[3] and others. This theory interprets the anomaly as an aberration of the usual migration of the embryonic pancreatic anlagen. These normally appear in the 4-mm. embryo as paired ventral buds arising in the caudal angle between the foregut and the liver diverticulum and single third outgrowth into the dorsal mesentery. Elongation of the bile duct and unequal growth of the duodenal wall lead to rotation of the ventral pancreatic anlagen posteriorly and to the left, with eventual fusion to the dorsal pancreas during the seventh fetal week. According to Lecco, the tip of the ventral pancreatic bud may become adherent to the duodenal wall, and when the normal migration of its base occurs, the duodenum becomes encircled by a band of pancreatic tissue (Fig. 1 and 2).

Thus, when this anomaly is discovered on surgical exploration or at the autopsy table, the second part of the duodenum is seen to be banded and usually obstructed by a narrow strip of pancreatic tissue. This is usually a complete ring that is inseparable from the head of the pancreas, but in some cases there has been

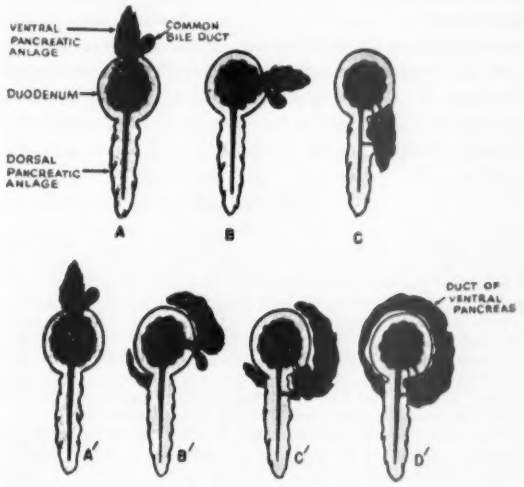

FIGURE 1. *Diagrammatic Outline of the Development of the Common Bile Duct, Pancreas, Main Pancreatic Duct (Wirsung) and Accessory Pancreatic Duct (Santorini)* (A, B *and* C), *and the Origin of the Annulus about the Duodenum from the Ventral Pancreatic Anlagen* (A, B *and* C).

a break in the continuity anteriorly. Grossly, the annular formation has the characteristic appearance of normal pancreatic tissue, and histologic study confirms this impression. The usual islet-cell and acinar-cell structures are noted, and almost always there is

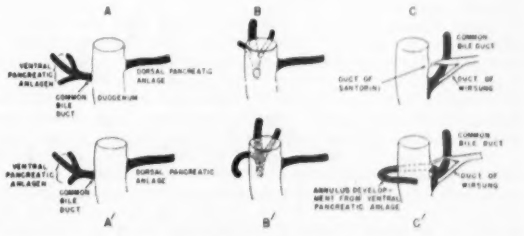

FIGURE 2. *Horizontal Section of Changes Outlined in Figure 1.*

A, B *and* C *represent the normal sequence, and* A, B, C *and* D *show the development of annular pancreas. Note the presence of a duct in the encircling band, which develops from the ventral pancreatic anlage. This is almost always present and probably accounts for the poor results accompanying surgical attack on the ring itself.*

a central main duct, which starts on the anterior aspect and courses to the right, posteriorly and then to the left to join the main pancreatic duct.

When the patient has lived beyond the newborn period the pathological changes that occur are as-

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sociated with an abnormality in the region of the pancreatic and common bile ducts. These include acute and chronic pancreatitis, dilatation and thickening of the duodenum about the constriction, gastric and duodenal ulcer and biliary-tract obstruction with jaundice. In early infancy, aside from other congenital malformations, which are frequent, the associated pathology is essentially that of duodenal and sometimes biliary-tract obstruction. These occur in degrees varying from little or no constriction to complete blockage of the duodenum, and there may or may not be common-duct compression with jaundice and secondary changes in the liver.

Case Report

G. (B.F.H. 17483), a 2-day-old male infant, was admitted to the hospital on January 25, 1952, because of vomiting. He was born after an 8-month pregnancy complicated by moderate vaginal bleeding at the 4th month, which subsided with bed rest. Labor and delivery were normal, anesthesia was not used, and the baby weighed 5 pounds, 12 ounces, at birth. Feedings were begun on the 2d day of life, and vomiting occurred a few minutes after each feeding. Bile was not noted in the vomitus, but coffee-grounds material was described on one occasion.

Physical examination revealed a small baby weighing 4 pounds, 5 ounces, with a good cry and in no apparent distress. He was moderately dehydrated, and there was slight cyanosis of the hands and feet. The heart, lungs and abdomen were normal. Rectal examination revealed a moderate amount of normal meconium, which showed desquamated squamous cells on microscopical examination. Urinalysis was normal. The white-cell count was 15,600, with a normal differential; the red-cell count was 5,320,000, with a hemoglobin of 22 gm. per 100 cc., or 140 per cent by the Sahli method. The blood electrolyte values were as follows: sodium, 142 milliequiv., potassium, 5.4 milliequiv., chloride, 96 milliequiv., and carbon dioxide 22 milliequiv. per liter. The nonprotein nitrogen was 46 mg. per 100 cc.

The baby was placed in a heat-controlled bed, and appropriate fluid therapy begun intravenously. X-ray examination of the abdomen showed absence of gas distal to the dilated 2d portion of the duodenum (Fig. 3), indicating complete duodenal obstruction.

On the 3d day of life operation was performed. The stomach was emptied through a Levin tube, which was left in place during surgery. The abdominal wall was then infiltrated with 1 per cent novocain, and the abdomen opened through a high right-rectus-muscle-retracting incision. The stomach and the 1st portion of the duodenum were markedly distended, but gas could be expressed into the jejunum. More distally the small intestine and the large bowel appeared normal although collapsed. The hepatic flexure was mobilized, and the colon turned medially. Veil-like bands on the anterolateral surface of the duodenum were divided to expose and visualize the duodenum distal to the obstruction. The 2d portion of the duodenum was encircled by a ring of glandular tissue approximately 1 cm. in width and continuous with the head of the pancreas. Thus, it was obvious that the duodenal obstruction was due to an annular constricting pancreas. A posterior duodenojejunostomy was performed, the dilated 1st portion of the duodenum and a loop of jejunum approximately 6 to 8 cm. from the ligament of Treitz being used.

The postoperative course was uneventful. Fluids were given intravenously during the 1st 3 days after operation, during which gastric aspirations were performed every 8 hours. The amount obtained by aspiration rapidly diminished, and feedings were begun on the 4th day. These were gradually increased so that by the 7th day the patient was taking a full and adequate formula. He gained well and was discharged from the hospital on the 11th day after operation weighing 5 pounds, 12 ounces. Stools were of normal color and consistence. On follow-up examination 1 year later he appeared normal in development. There were no symptoms referable to the operation, and x-ray examination showed a normally functioning anastomosis.

Discussion

As mentioned above, this anomaly may be present with few or no associated symptoms. When manifest in infancy the clinical picture is that of duodenal obstruction. Thus, there is vomiting, distention and obstipation, the severity depending on the degree of blockage. There may or may not be bile in the vomitus. If the obstruction is of a relatively low grade the symptoms may be intermittent, and the tympanites much less marked.

Figure 3. *Anteroposterior Film of the Abdomen, Taken in the Recumbent Position, Showing Multiple Peristaltic Waves in the Stomach and Gaseous Distention down to the Mid-portion of the Descending Duodenum.*

Elsewhere in the abdomen there is complete absence of gas, and the appearance is diagnostic of complete duodenal obstruction. Barium study was unnecessary and contraindicated.

X-ray examination by means of films of the abdomen in the recumbent and erect positions usually establishes the presence of duodenal obstruction. The stomach and first part of the duodenum are markedly distended by gas, which ends abruptly at a variable level in the mid-descending portion of the duodenal loop. If obstruction is complete gas elsewhere in the abdomen is sparse or absent. But the prominence of the radiographic findings varies, as does the symptomatology, with the degree of duodenal constriction. Thus, one may see all gradations from complete absence of gas below the mid-duodenum to a nonspecific, negative x-ray study of the abdomen. In the presence of the latter the next diagnostic maneuver is a barium-meal examination, which will demonstrate the abnormal duodenal contour. The barium passes readily into a dilated cap and proximal duodenum and then outlines a localized constriction, which is usually seen at the midlevel of the descending segment. Distally, the gut appears normal. In the presence of x-ray evidence of complete or high-grade duodenal obstruction the barium study is unnecessary and contraindicated since it can only serve to aggravate the symptoms.

Beyond the demonstration of complete or partial duodenal obstruction the x-ray studies are not specifically diagnostic. The differential diagnosis must include, besides annular pancreas, duodenal stenosis or atresia and midgut malrotation. In the last condition obstruction may be complete or partial and intermittent and results from encroachment on the duodenum by a mesenteric band, or in some cases, the cecum itself.

With the establishment of mechanical duodenal obstruction surgical intervention is obviously mandatory. The situations that may be encountered have already been discussed. At exploration, after the duodenum has been exposed, the nature of the anomaly is readily demonstrable. The annular constricting band is seen to consist of glandular tissue continuous with that of the pancreas. Once this situation has been recognized, the proper treatment is a surgical by-pass procedure. In the past, direct attack on the ring has led to a high incidence of complications. These have included pancreatic fistula, pancreatitis and recurrence of obstruction caused by scarring at the site of operation. Therefore, the procedure of choice is considered to be a duodenojejunostomy. This allows for maintenance of the integrity of the pylorus and results in normal physiologic alimentation. If concomitant and complete obstructive jaundice is encountered internal biliary decompression must also be performed. This situation has not been described in any of the reported cases.

Summary

A successfully treated case of congenital annular pancreas causing duodenal obstruction is presented. Embryology, diagnosis and treatment are described.

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BY THE LONDON POST

Doctors and Clergy — Women Graduates

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A PATIENT with anxiety symptoms came to my clinic a few weeks back, and I asked her whether the tablets I had prescribed (barbiturates) were doing her any good. She answered with some hesitation that she thought they had helped her and then added quickly, "But they've not done me as much good as Dr. Billy Graham." I have no doubt that she was quite right.

The importance of the spiritual element in a properly integrated physical and mental life has recently been stressed in a number of letters to the *British Medical Journal*. The correspondence was opened by a Church of England clergyman who asked for closer co-operation between the church and the medical profession, without which neither could do its appointed work in the healing of the "whole man." Many doctors have endorsed this view and welcomed the upward thrust of the spiritual in medical as in many other walks of life. One writer suggested that in treating many cases it would be ideal if a doubly qualified priest-doctor were available. Indeed, an advertisement recently appeared for a doctor in the north of Scotland who "if possible, should also be a Presbyterian minister of religion."

Such double qualifications must be rare, but it is most interesting that the British Medical Association has appointed a committee to prepare evidence for a Commission on Divine Healing, which has been set up by the archbishops of Canterbury and York. The commission will consider the theologic, medical, psychologic and pastoral aspects of "divine healing" and will also endeavor to encourage greater co-operation between the clergy and the medical profession.

The British Medical Association committee, to enable itself to submit its evidence to the commission, has drawn up a questionnaire that any doctor with special knowledge or definite views is invited to complete (*Brit. M. J.* **1** [Supp.]:294, 1954). The first part includes questions relating to divine healing that ask for first-hand information about cases in which a patient has recovered from an apparently incurable disorder, either with or without some spiritual ministration, with direct questions about the nature of the recovery (healing services, the laying on of hands, unction or the effect of pilgrimages). Information is also sought whether such practices have been attended by harmful effects, such as the risk of delay in seeking medical advice.

The questions are directed to doctors' views on the value of the minister or priest in assisting a patient's attitude toward his illness, convalescence and rehabilitation, and to the further measures, if any, that should be adopted to promote closer correlation.

It is clearly of the utmost importance to have honest and unbiased thinking on the subject. It is also clear that the degree of mutual assistance that develops will greatly depend on individual personalities. Indeed, one wonders whether the emphasis on the need for co-operation between the doctors and clergy is another reflection on the present-day trend toward specialization. Surely, in days gone by, although the family doctor may not have been "doubly qualified," he undoubtedly acted as a family counselor and friend, and often ministered not only to the body but also the soul of the patient.

* * *

It is interesting to recall that Elizabeth Blackwell, the first American woman to receive a medical degree,

was also the first woman on the British Medical Register. A native of Bristol, she emigrated with her parents and received her medical degree at Geneva, New York, in 1849. She later returned to England and was practicing in London when the register was formed under an Act of Parliament in 1858. At that time no woman was admitted to a medical school in this country, and it was a long struggle before Elizabeth Garrett Anderson, in London, and Sophia Jex-Blake, in Edinburgh, succeeded in their endeavors to become doctors. It was largely as the result of their efforts that the London School of Medicine for Women was established in 1874 and that women were admitted to the Edinburgh school. There, the early days of the women students were far from easy. On one occasion, when a woman won a chemistry scholarship, the whole faculty was horrified and, headed by the professor of chemistry, attempted to turn the new students from the university. On another occasion a famous riot occurred when Sophia Jex-Blake and her friends were pelted with mud and vegetables by the male students, who thought they were expressing their intellectual superiority.

The complete acceptance of women in medicine took almost a century, and it was not until 1947 that every medical school in the country opened its doors to women students. In fact there are still many difficulties confronting a young woman wishing to study medicine, for, although there are now about 10,000 women on the Medical Register, there are only a relatively small number of places available to them in the medical schools each year.

There are those who regard such discrimination as reprehensible, but others consider it in the best interests of the general public. They argue that the number of students who can be taught is limited by teaching facilities and believe that the preference given to men is fully justified so long as a large proportion of women doctors give up full-time practice, generally on marriage, within a few years of graduating. There is no doubt that this is a powerful argument, and the effect of marriage on the careers of all women with academic qualifications has recently been exercising the minds of university teachers. The results of one survey on the subject have been presented in a study entitled "Graduate Wives" (*Planning* **20**:21-44, 1954), in which 1165 married women graduates and 420 married women of similar age with no university training completed a questionnaire. Of the women graduates only 1 per cent said they would not go to a university again if they had the chance, whereas 75 per cent said they would study the same subjects. In comparison, only 52 per cent of the nongraduates admitted satisfaction with their education. Furthermore, marriage had ended the planned careers more often among nongraduates than among graduates. Fifty-three per cent of the wives who had graduated were able to undertake part-time or whole-time paid work, whereas only 20 per cent of those who had not graduated were able to do so. These figures suggest that married women with an academic training are giving a good account of themselves, but in medicine it cannot be disputed that marriage removes many women with careers of promise from the active ranks. This was stressed by Dr. Annie Gillie, president of the Medical Women's Federation, in her presidential address. A young woman requires determination and character to overcome the impediments to her professional career caused by marriage, but Dr. Gillie regards the problems as new challenges that must be accepted.

Commenting on this vexing question the *Lancet* points out that the dividends from education cannot be assessed in terms of paid work and believes that education is never wasted. The trained mind and the cultured outlook are assets that cannot be measured easily, but they make a great, indirect contribution to family life and to the life of the nation.

CASE RECORDS
OF THE
MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 40301

PRESENTATION OF CASE

A seventeen-year-old male student entered the hospital because of weakness and difficulty in speaking and swallowing.

About two months before admission the patient, previously in good health, began to feel generally weak and found that he tired easily. The weakness, at first especially apparent to him when he climbed stairs, gradually progressed but was not noticed by his parents until they became aware of a nasal quality to his voice about a month before admission. Three weeks before admission, while walking into the ocean with the intention of swimming, he suddenly fell and was unable to rise. He was helped up by friends and shortly afterward was able to walk home, but that evening he fell on the street. During the next week the weakness progressed, becoming more severe on the right than on the left, so that he could not bear weight on his right leg and was unable to hold a pen in his right hand. His speech became more nasal in quality, and he began to have difficulty in swallowing. Two weeks before admission he entered another hospital, where he was found to have blurring of the optic disks, facial asymmetry, nasal speech, impairment of swallowing, weakness of the right arm and leg, bilateral extensor plantar reflexes and intact sensation. Lumbar puncture showed the cerebrospinal fluid to be under an initial pressure equivalent to 200 mm. of water, and the cerebrospinal fluid contained 200 crenated red cells per cubic millimeter, no white cells and a total protein of 49 mg. per 100 cc. Lumbar puncture four days later revealed a pressure equivalent to 130 mm. of water; the spinal fluid contained 32 crenated red cells per cubic millimeter and no white cells, and the total protein was 30 mg. per 100 cc. A prostigmine test produced no improvement in strength. X-ray study of the skull and chest, an electrocardiogram and routine blood and urine examinations were all negative. Meanwhile, the weakness steadily progressed. Two days before admission he complained of bifrontal headache for the first time. Throughout the development of the illness there had been no nausea, vomiting, anorexia, impairment of consciousness, involuntary movements or sphincter disorder.

The patient had had no significant or pertinent previous illnesses. The family history was not remarkable.

General physical examination disclosed a well developed and well nourished boy; no significant abnormalities were noted. On neurologic examination he was alert, intelligent and co-operative. There was blurring of both optic-disk margins, with good visual acuity and no field defect. Ocular movements were full, and there was no nystagmus. Sensation of the face, including the corneal reflexes, was normal. There was slight facial weakness on the right, with sagging of the right corner of the mouth. Taste and hearing were normal. The gag reflex was present bilaterally, but weak. The voice was nasal in quality. He swallowed water without difficulty. The tongue deviated to the left on protrusion, with questionable slight left-sided atrophy. There was generalized weakness of the trunk and of all limbs so that he could not sit up, stand or walk without help. Weakness was generally greater on the right than on the left, except that the left triceps was weaker than the right. There was no voluntary movement of the right ankle and toes. The jaw jerk was abnormally brisk. Tendon reflexes were more active on the right than on the left; they were sluggish to absent in the arms but brisk in the legs, and there was bilateral ankle clonus. The abdominal reflexes were present. The plantar reflexes were extensor. Sensory examination was negative. Co-ordination, as indicated by the finger-to-nose and heel-to-shin tests and performance of rapid alternating movements, was considered normal, except as impaired by weakness. There was no nuchal rigidity or Kernig sign.

The temperature was 98.6°F., the pulse 80, and the respirations 24. The blood pressure was 122 systolic, 80 diastolic.

Urinalysis was negative. The white-cell count was 9800, with a normal differential. On the third hospital day the cerebrospinal fluid contained 1 red cell and 1 white cell per cubic millimeter; the total protein was 48 mg. per 100 cc., and the colloidal-gold curve was normal. The spinal-fluid Hinton test was negative. Another lumbar puncture on the seventeenth hospital day showed a pressure equivalent to 420 mm. of water; the spinal fluid contained 2 lymphocytes per cubic millimeter, and the total protein was 57 mg. per 100 cc. An electroencephalogram was reported as normal. A pneumoencephalogram on the third hospital day, with 20 cc. of air, was unsatisfactory.

While the patient was in the hospital definite papilledema developed. At times he was unco-operative, and his mood was observed to be labile. A disproportionate degree of ataxia and clumsiness in the use of the left arm also developed. His speech became less understandable, and the difficulty in swallowing became pronounced. On the nineteenth hospital day he wept loudly and hysterically for forty-five minutes. This was immediately followed by an outcry and what was thought to be a generalized tonic seizure in which there were flexion of the left arm and right leg, turning of the eyes to the right and chewing movements of the left side of the mouth. The episode lasted about ninety seconds, after which he was unresponsive. Opisthotonos and extensor postures of the hands, subsequently developed. He was taken to the operating room, where the ventricles were tapped, and ventriculography was performed (Fig. 1). During this procedure he went into respiratory arrest, with widely dilated pupils. Posterior-fossa exploration and cerebellar decompression were then performed. Besides compression of the cerebellar tonsils at the foramen magnum no abnormality was seen. Spontaneous respirations never returned, and he was kept in a respirator until he died five hours after operation.

Differential Diagnosis

Dr. Derek E. Denny-Brown*: The problem we are presented with concerns the insidious onset of generalized weakness and fatigability in a young student. The symptoms were largely subjective, and others noticed only a nasal quality in his voice. In the fifth week of the illness sudden failure in the strength of the lower limbs led to two falls, with inability to rise after one of them. Sudden collapse of the lower limbs of this kind suggests a bilateral weakness of the quadriceps muscles. An examination in the next week, the sixth week of the illness, disclosed a spastic type of weakness of the right arm and leg, with bilateral extensor plantar responses. There was now some evidence of bulbar damage in the form of difficulty in swallowing as well as nasal speech. At the same time blurring of the optic disks was discovered and suggested increased intracranial pressure. The first lumbar puncture revealed a high borderline pressure and a second puncture a low pressure, presumably leaving some doubt in the minds of the physicians taking care of the patient. The first spinal fluid contained a few red cells, apparently recent, and a slight rise in protein, but none of these findings were confirmed in the second lumbar puncture four days later. Only the appearance of bifrontal headache two days before admission, with steady progression of the weakness, again called attention to the possible increase of intracranial pressure, although vomiting and nausea were still absent. Examination now revealed a severe weakness in all limbs, with no voluntary movement at all in the right leg. This weakness was spastic in type and more obvious in the legs than in the arms, and there was some difficulty in obtaining tendon reflexes. Again, no sensory disturbance was found. There was no inco-ordination.

Attention is particularly called to the abnormalities found in the cranial nerves because the history of difficulty in speaking and swallowing points unmistakably to brain-stem damage. Only a slight facial weakness on the right, presumably of central type, slight weakness of the left side of the tongue and weak gag reflex were noted. I suspect that the palate moved weakly, but the nasal voice is the only evidence of this. The ability to swallow water without difficulty certainly indicates that the defect in swallowing was not severe. The history of these symptoms was so recent that even slight left-sided atrophy of the tongue was probably significant. The brisk jaw jerk certainly suggests bilateral damage at the pontine level or higher. The presence of papilledema was confirmed, and another lumbar puncture revealed a greatly increased cerebrospinal-fluid pressure with a rising protein content, but normal cell count. The good visual acuity, intact visual fields and general alertness indicate that general central function was as yet not impaired.

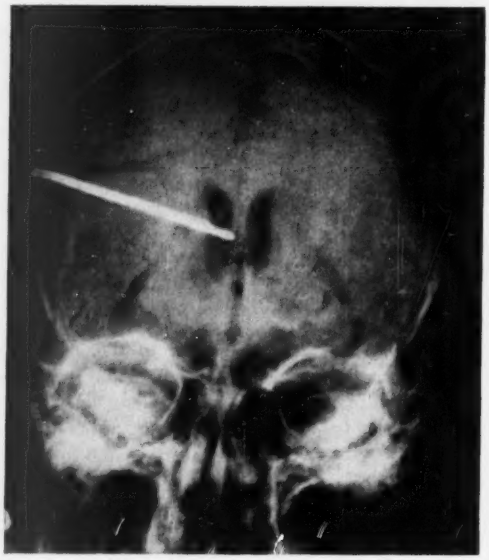

Figure 1. *Ventriculogram, Anteroposterior Projection.*

Physical diagnosis in disease of the nervous system can usually follow a more logical sequence than that in disease of other organs, because it can proceed first to a fairly precise anatomic localization, and this considerably narrows the range of possible pathologic processes. In this case there are difficulties with the anatomic localization, long before we can get to the point of discussion of possible diseases. It is clear that

*James Jackson Putnam Professor of Neurology, Harvard Medical School; director, Neurological Unit, Boston City Hospital.

the patient was suffering from some kind of impairment of function of the corticospinal tracts bilaterally in association with damage to the corticobulbar fibers; therefore, the process must have been at a point where all these structures lie close together. The disturbance must have spared the midbrain, for the extraocular nerves were not involved, and must have been more severe on the left side, so as to affect the right arm and leg more severely. It possibly involved the left twelfth nerve, and it must have been so situated as not to damage sensory pathways. The absence of strabismus or nystagmus makes it extremely unlikely that the pontine tegmentum was involved, for these are reliable signs of damage to dorsal parts of the brain stem. No cerebellar signs were noted. The absence of vomiting excludes a primary lesion in the fourth ventricle.

Attention is diverted from the cerebellum and brain stem itself and from disorders arising in the lateral recess of the posterior fossa, which, in general, disturb the cranial nerves that make exit in that situation so that the absence of facial paralysis, deafness, fifth-nerve weakness and loss of corneal reflex are valuable excluding signs. We are therefore led to think in terms of processes that affect the anterior aspects of the brain stem, displacing it backward and first damaging the motor tracts and later leading to obstruction of the circulation of cerebrospinal fluid. Our impression that this was the real situation of the disorder is reinforced when we find that ataxia and clumsiness of the left arm eventually appeared during the hospital stay, indicating that the left side of the pons was ultimately damaged although not primarily affected. A pseudobulbar emotional disorder resulting from the bilateral corticospinal damage was also a late sign. This was followed by a tonic seizure in which the attitudes were those of severe upper-pontine damage on the left side, leading to the severe crisis with the failure of respiration and widely dilated pupils that document herniation of the cerebellum at the foramen magnum.

The consideration of pathologic processes that could lead to this disturbance of function must take into account the steady evolution of the whole illness in the course of eleven weeks. The previous history offers no clues. General examination gave no evidence of a generalized process. Laboratory examinations offered no significant additional evidence. It is clear that the process was an expanding one, and the repeated cerebrospinal-fluid examinations failed to reveal any inflammatory process or hemorrhage. I shall discount the few cells noted in the first lumbar puncture. The anterior aspect of the brain stem is an unusual situation for primary gliomas of the nervous system. The usual glioma in this situation, glioma pontis, grows much more slowly, and the rapidity of evolution also excludes hemangioma or other types of tumor in the brain stem itself. One is therefore led to think of tumors of the base of the skull; the chordoma of the basiocciput is more malignant than meningioma and occasionally grows back into the posterior fossa, but I should expect such a tumor to damage the sixth nerves and to lead to bony erosion that could be seen in the x-ray films.

May I see the films of the skull?

Dr. John F. Gibbons: I have only films of the ventriculogram that were taken when the patient was brought to the operating room. Here is the lateral projection of the skull.

Dr. Denny-Brown: I should expect the films to show dilatation of the lateral and third ventricles. They are in fact not greatly dilated even near the terminal crises when the intracranial pressure was obviously increased. I think this large, sharp shadow in the posterior fossa is the outer edge of a large ethmoid air cell, and I agree that there does not appear to be any significant change in the base of the skull. My inclination is now toward some lesion in the posterior fossa and not the base of the skull. The sphenoid ridge is rather thin, and there is a large sphenoid sinus, but I do not see anything very significant in that view.

Dr. Gibbons: The radiologist who interpreted these films raised the question of a little more tissue between the lateral ventricles in the sagittal projections than one usually sees (Fig. 1). Do you consider that significant?

Dr. Denny-Brown: The ventricles in that anteroposterior view are narrower than usual and have lost their butterfly appearance. They appear to be separated by a broader septum pellucidum than normal.

Certainly, a patient who had an obstruction of the posterior fossa should have widely dilated ventricles and a thin septum pellucidum. I am not able to bring these findings into line with anything in the history of this patient. That is my difficulty. I do not find anything in the history or findings that calls attention to any supratentorial region. The basal cistern interests me particularly, but I do not see anything there to give me any clue.

In the absence of any signs of bony erosion of the skull I begin to think of other possibilities in relation to this anterior aspect of the brain stem. The next possibility that I should consider is an abnormality in the basilar artery. The usual fusiform aneurysm of the basilar artery affects much older patients. It is an arteriosclerotic aneurysm, which gives signs of chronic traction on the cranial nerves. I should think it is impossible for this to have been a fusiform aneurysm of the basilar artery, but the basilar artery may be the site of a congenital aneurysm, a large rounded mass that takes origin on the front of the brain stem and can displace it backward considerably. That possibility appeals to me more. The difficulty in relating it to the present story is the steady evolution of the symptoms over a period of eleven weeks, but a congenital aneurysm of the basilar artery would account for the clinical disturbance in this patient much better than any other possibility that I have mentioned.

After that I should have to cast around among extremely rare conditions to find a possible explanation for the evolution of a pathologic process in this situation over such a brief period. The radiologist's observation about the septum pellucidum makes me wonder whether I am wrong about the anatomic situation of this lesion, but I am convinced that the story could only be explained by progressive impairment of the base of the brain stem itself, particularly the disturbance of voice and swallowing. I have to admit the alternative possibility of a glioma that affected the anterior part of the pons. That is to me the less satisfactory of the suggestions that I can make, and I think I had better leave it at that. Of the series of unlikely possibilities I should think the least unlikely is congenital basilar aneurysm and next a gliomatous tumor of the pons.

DR. JAMES B. AYER: Do you think a supratentorial tumor is indicated by the convulsion? Do you think that there was a focal seizure although it was one arm and the other leg?

DR. DENNY-BROWN: I should be unwilling to call the attack a focal seizure.

DR. BENJAMIN CASTLEMAN: Dr. Adams, you saw this patient; would you tell us the impression on the ward?

DR. RAYMOND D. ADAMS: Yes; I saw this patient shortly after he came in. We were impressed by the bilateral pyramidal-tract signs, slurred speech and difficulty in swallowing, so that we had the impression, as Dr. Denny-Brown did, that this process was localized to the brain stem. As time went on, however, it seemed surprising that more definite cranial-nerve signs did not turn up. Our differential diagnosis before the seizure and the signs of increased intracranial pressure had appeared was between a demyelinating disease and a neoplasm; later, we believed that neoplasm was more likely. Furthermore, when the final quadriplegia developed, we assumed that the cerebellar tonsils had herniated down through the foramen magnum. The whole case was unusual, and we were surprised by the nature of the process that was finally revealed to us, but even more by its locality. I must say that we tried to visualize the fourth ventricle, but we could not get air into it.

DR. V. MARK: I have only one comment about the operative procedure in addition to what was mentioned in this record. About 20 cc. of clotted blood between the arachnoid and cerebellar tonsils was evacuated. I thought that there was definite molding of the cerebellar tonsils at the time of operation. The floor of the fourth ventricle was visualized, and it appeared normal. I wonder if Dr. Ballantine would like to comment about the events leading up to the operation.

DR. H. THOMAS BALLANTINE: It was a hot day in August, and in the afternoon we heard that this patient was scarcely breathing, had increased intracranial pressure and was in extremis, with extensor rigidity. We did not believe we were justified in carrying out any operation until after we had a little better localization by air studies so we put in a burr hole. The first study was unsatisfactory, and we then put a catheter into the ventricles and got what we thought were fairly satisfactory films; they still did not tell us where the lesion was, however. The fact that both pupils were widely dilated made us believe that it was unlikely that there was a herniation of one temporal lobe through the notch of the tentorium. We decided the only way to try to remedy this desperate situation was to decompress the posterior fossa. I well remember that while we were sitting in the x-ray conference room one observer made the comment that if the patient had not had all those brain-stem signs, the finding in the x-ray film would suggest that he had a glioma of the corpus callosum and perhaps of the septum pellucidum as well.

CLINICAL DIAGNOSES

Pontine neoplasm.
Cerebellar pressure cone.

DR. DEREK E. DENNY-BROWN'S DIAGNOSIS

Progressive damage to brain stem: ?glioma of pons; ?congenital aneurysm of basilar artery.

ANATOMICAL DIAGNOSIS

Glioblastoma multiforme of corpus callosum, both cerebral hemispheres and brain stem (gliomatosis cerebri).

PATHOLOGICAL DISCUSSION

DR. EDWARD P. RICHARDSON, JR.: The relevant findings in this case were confined to the central nervous system. We are very grateful to Dr. Denny-Brown for a most interesting discussion of the diagnostic possibilities.

This was a case that surprised everyone. It was an example of an extremely unusual condition that we have rarely seen here. On gross examination the corpus callosum and septum pellucidum were observed to be thickened and gray, and the cerebral white matter generally to be abnormally firm, especially on the left side. These findings are best illustrated by a series of stained sections (Fig. 2 and 3). Low-power views of sections stained for myelinated fibers showed some pallor of staining in the affected areas but, in general, good preservation of cerebral architecture and of many of the nerve fibers. Higher magnification revealed diffuse infiltration of the entire brain by neoplastic cells, which could be found in all parts of both cerebral hemispheres. The densest collections of these cells were in the corpus callosum and central white matter, but there were no areas of white or gray matter in the cerebral hemispheres in which they could not be found. There were large numbers of neoplastic cells in the internal capsules and the cerebral pedun-

cles, and a few of these abnormal cells could be seen in the pons and in the pyramidal tracts and middle cerebellar peduncles. No neoplastic cells were found in

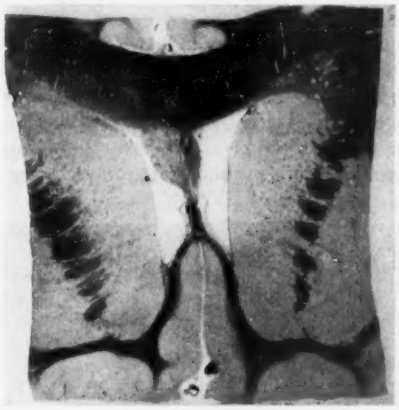

FIGURE 2. *Coronal Section of the Brain at the Level of the Putaminocaudate Junction (Loyez-Myelin Stain, Low Power). The corpus callosum is thicker than normal and abnormally pale, and the septum pellucidum is irregularly thickened.*

sections of the medulla oblongata and cerebellar cortex. The microscopical features of the neoplasm were

FIGURE 3. *Coronal Section at the Level of the Anterior Thalamus (Loyez-Myelin Stain, Low Power). Note the marked thickening and pallor of the corpus callosum, and the pallor in the brain generally on the right side (left in photograph), with preservation of the architectural outlines.*

seen in a high-power view of the corpus callosum (Fig. 4), in which there was dense infiltration with cells that varied greatly in size and shape and frequently contained multiple or stangely contorted nuclei. In its histologic details the tumor was typical of glioblastoma multiforme and must so be classified, but the neoplastic involvement of the brain was so extensive that this case belongs with other rare cases that are called gliomatosis cerebri.

DR. DENNY-BROWN: I still wonder how the bulbar symptoms arose. Dr. Richardson, have you any notion about that?

FIGURE 4. *Tumor Infiltration of the Corpus Callosum (Cresyl Violet Stain, High Power). Note the dense cellularity and variation in the nuclear size and shape.*

DR. RICHARDSON: There was so much involvement of the entire brain by the time we saw it that it is difficult in retrospect to relate the clinical manifestations to the pathologic findings with any exactness. We considered that the bulbar manifestations might be due to the infiltration by tumor tissue of both internal capsules and both cerebral peduncles, resulting in pseudobulbar paralysis.

DR. DENNY-BROWN: There was infiltration of the pons. I suppose it was difficult to tell where the greatest effect on physiologic function occurred.

DR. RICHARDSON: Extremely so. The tumor had invaded everywhere except the cerebellum and medulla.

CASE 40302

PRESENTATION OF CASE

A seven-month-old male infant was admitted to the hospital because of vomiting, diarrhea and an abdominal mass.

The patient had been well without significant past illnesses or feeding difficulties until a week previously, when he had a watery stool unassociated with any other signs or symptoms. The next day he had two loose, foul stools, but again no abnormal physical

findings were observed. He seemed well, and bowel movements were normal during the next four days; however, two days before admission irritability and fever developed, and he vomited once. He did not seem to have abdominal pain but did have one loose stool. A physician gave him an injection of penicillin for "pharyngitis," after which the fever disappeared. During the day before admission he vomited three to five times, refused feedings and had two loose stools. There was no fever and no apparent colic. On the day of admission the physician found the patient dehydrated, with a mass in the abdomen, and advised hospitalization. On this day there had been no vomiting, fever, abdominal pain or diarrhea. One bowel movement on admission, however, consisted of copious, yellow, guaiac-positive material. The parents had not noted evidence of blood in any of the stools since the onset of the illness.

The patient was the product of a full-term normal delivery. Although the details were not known, he had apparently been given fluids intravenously, when he was three or four days old, because of dehydration. He had not had any of the contagious diseases and apparently had not recently been exposed to them.

Physical examination showed a well developed and well nourished but poorly hydrated infant in no acute distress. The right eardrum was red and bulging, and the left red but with good landmarks; there was no discharge. There was moderate hyperemia of the pharynx. The heart and lungs were normal. In the abdomen there was no spasm, rigidity or tenderness, and the liver edge was just barely palpable. There was a left-sided, midabdominal fusiform mass extending from just to the right of the umbilicus laterally to the left flank, with the widest diameter at the midclavicular line. The mass seemed to be firm and nontender; it did not move with respiration, nor was it fixed to the anterior abdominal wall. It was movable to the extent that it could be pushed to the right of the umbilicus and a hand could be introduced above it superiorly but only questionably in the posterior flank. Peristalsis was normal. Rectal examination was negative.

The temperature was 101°F., the pulse 150, and the respirations 30.

Urinalysis demonstrated a specific gravity of 1.001 and gave negative tests for albumin and sugar; the sediment contained 0 to 3 white cells and a rare red cell per high-power field. Examination of the blood revealed a hemoglobin of 13.5 gm. per 100 cc. and a white-cell count of 11,100. The serum sodium was 140 milliequiv., the potassium 4.0 milliequiv., the chloride 102 milliequiv., and the carbon dioxide 27 milliequiv. per liter. A stool specimen passed on admission gave a + + + guaiac reaction, but two other examinations later during the same day were negative. Roentgenograms of the chest and skull were normal. An intravenous pyelogram disclosed a mass about 7 cm. in diameter in the left midportion of the abdomen whose medial border could not be distinctly made out. During the examination it was always seen to the left of the midline except once, when it appeared to be a little more medially placed. The descending colon was reduced in size, but the rest of the bowel did not appear affected. The left kidney could be visualized in its normal position on one film and appeared to be separate from the mass (Fig. 1). The right seemed slightly lower in position, and both showed good excretion of the dye. The calyxes did not reveal anything abnormal although the lowest calyx on the left was not so clearly seen as the others. The medial portion of the left ureter was more medially placed than usual but was not definitely displaced. The bladder appeared normal.

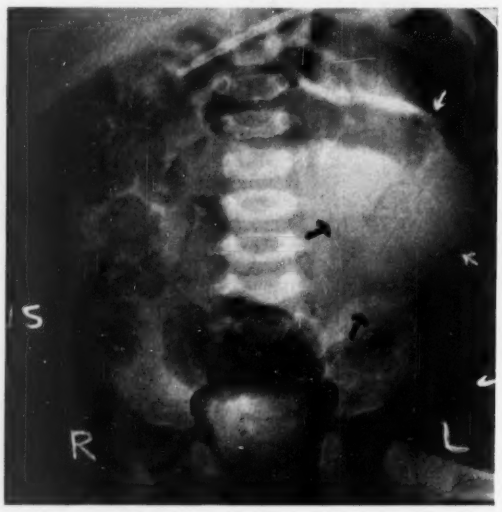

FIGURE 1. *Intravenous Pyelogram.*
Arrows outline the mass in the left side of the abdomen, which in the original films appeared to be separate from the kidney; the proximal left ureter is displaced medially.

In the hospital the patient was given fluids intravenously, and a gastric tube was passed. On this regimen there was no further vomiting or diarrhea, and the abdomen remained soft. There were no striking clinical changes, and he seemed somewhat brighter although the temperature remained at levels of 99°F. On the second hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. JOHN W. RAKER*: I should like to know whether a barium-enema examination was done.

DR. JOSEPH HANELIN: None was done.

DR. RAKER: I shall discuss the case first and have Dr. Hanelin help us with the x-ray evidence later. This might have been a disease caused by something extraperitoneal, but I think this is quite unlikely. The

*Assistant in surgery, Massachusetts General Hospital.

only thing that suggests that is the questionable displacement of the left ureter. That is not very impressive in the record, and I think that there was probably nothing wrong with the kidneys or any other retroperitoneal organ. Within the peritoneal cavity the condition could have been outside the gastrointestinal tract. I should not be too surprised if this was an omental cyst or a mesenteric cyst although the fact that the patient had symptoms makes me think of other conditions.

It is more likely that this was associated with the gastrointestinal tract. I can eliminate a number of conditions at once because of the age of the patient; since he was not in the neonatal period and had no real evidence of obstruction I can throw out as most unlikely any form of atresia or stenosis of the gastrointestinal tract. Malrotation is probably excluded by the x-ray report, which described the descending colon as being in a more or less normal position, and by the fact that the typical story of recurring attacks was lacking. I cannot exclude the possibility that the bleeding was caused by polyps within the gastrointestinal tract, but I do not think that it is likely. That leaves me three major diagnoses to consider: intussusception, Meckel's diverticulum and duplication of the intestine.

Intussusception, I think, is the least likely of the three. Incidentally, intussusception may be caused either by a Meckel diverticulum or a duplication. The age group is all right, and the fact that the mass was nontender is not inconsistent with an intussusception. However, there was no pain,—this is stated repeatedly in the protocol,—and the absence of pain is against intussusception. It is said that only 10 per cent of the patients with intussusception are free from pain. The fact that there had been no real evidence of continuing obstruction is aiso against intussusception. It is said that only about 15 per cent of patients with intussusception do not have clinical obstruction. The fact that there was blood in the stool is certainly compatible with an intussusception, but the type of hemorrhage is not quite characteristic. Typically, the patient should have passed one or two normal stools, and all the stools thereafter should have contained blood because the colon below the intussuscepting mass was cleansed of the nonbloody fecal material and the material that came down from the intussusception itself should have contained blood. In this case the bloody stool appeared first, and then there was no more blood. Perhaps this is not an important point, but it is against intussusception. The patient had a large mass, and yet he was not very sick. He was observed for about twenty-four hours in the hospital, and during this time he did not become terribly ill. The delay before operating, I gather from the protocol, was not to correct an extensive dehydration but because of lack of worry about him. One would expect an infant with an intussusception as large as this mass to have become increasingly ill as twenty-four hours passed. One more point is that rectal examination in an infant of seven months might very well have reached the leading end of an intussusception if it had been lying on the left side of the abdomen; if the small bowel had intussuscepted through the transverse colon and had been in the descending colon it might have been possible to reach the mass with the examining finger in the rectum. The fact that the rectal examination was negative, then, is another point against intussusception.

Meckel's diverticulum is perhaps more likely. The age group is all right. The fact that there was no pain does not rule it out because Meckel's diverticulum may be painless. Certainly, it may be painless if the only symptom is bleeding or if there is no obstruction. However, pain probably would have been present if an intussusception had developed as a result of the diverticulum. The bleeding from a Meckel diverticulum is often massive; this bleeding was not anything more than a small amount of blood in the colon and not a major hemorrhage. The fact that there was no obstruction is not inconsistent with a Meckel diverticulum. This mass was large, and it would have been unusual for a diverticulum this large to have been nontender. If a Meckel diverticulum is inflamed, one would expect not only that the mass would be tender but also that there would be more evidence of systemic infection. Although there was some fever, I suppose this evidence of systemic infection might be related only to the inflamed ears and the dehydration.

This brings me down to what I think is the most likely diagnosis—namely, duplication of the intestine. A duplication is defined as a cystic mass related and closely attached to the gastrointestinal tract, with two essential components—a muscle coat and a mucosal lining that is like the mucosa of some part of the gastrointestinal tract. Duplications are most commonly found in children up to the age of one although they may be found later. The fact that there was no pain is consistent with a duplication, with which there may or may not be pain; there is pain if the duplication causes obstruction or intussusception or if there is sufficient tension within the duplication itself to be painful. The blood in the stool is consistent with a duplication, for there may be hemorrhage from the distention of the nearby bowel or erosion of mucosal vessels overlying the duplication itself. The fact that there was no major obstruction is certainly consistent with a duplication. The description of this large mass, which was asymptomatic, nontender and mobile, impresses me as them most convincing evidence that the mass was a duplication. I should place this duplication in the small intestine or in relation to the small intestine although it could have been in the sigmoid. The only thing that worries me about this diagnosis—and it does not worry me too much—is that this child had apparently been examined in the past and the mass was not palpated. I am wondering whether the

infection of the ears caused the mild diarrhea, which may have called attention to the abdomen. Perhaps the mass was discovered when the abdomen was examined more carefully than it had been previously.

DR. WINFIELD S. MORGAN: Dr. Hanelin, would you like to show the x-ray films?

DR. HANELIN: I do not think the films will make Dr. Raker change his mind. The pyelogram does show a left-sided abdominal mass (Fig. 1). There is a suggestion that the outline of the left kidney can be differentiated from the mass although not clearly so. Considerable gas and fecal material in the large bowel obscure visceral outlines; the abdomen is quite distended. It does seem as though the descending colon outlined by gas and fecal matter is being pressed upon by the mass.

DR. RAKER: Can you see anything that gives you the impression that there is a good gas-shadow pattern around an intussusception?

DR. HANELIN: No; I do not see any evidence for intussusception, nor is there anything that suggests malrotation. Both kidneys are functioning, and there is no displacement of the calyceal systems. The left ureter may be displaced slightly toward the midline.

DR. E. STANLEY CRAWFORD: Dr. Raker, under what circumstances does one find a mass associated with a Meckel diverticulum in the absence of intussusception?

DR. RAKER: I can recall several patients in whom a large diverticulum could be palpated as an abdominal mass. We cannot exclude Meckel's diverticulum, but the ones I have seen have had a certain amount of local inflammation in their walls and the palpable mass was tender. That is why I put that diagnosis second.

CLINICAL DIAGNOSIS

Cystic tumor of small-bowel mesentery.

DR. JOHN W. RAKER'S DIAGNOSIS

Duplication of small intestine.

ANATOMICAL DIAGNOSIS

Duplication of small intestine.

PATHOLOGICAL DISCUSSION

DR. MORGAN: Dr. Crawford, will you tell us the opinion on the ward?

DR. CRAWFORD: Very soon after admission our impression was that the illness was due to the disease in the ears and throat and that the mass was incidental even though we could not be sure of it. The reason we did not operate until the next morning was, as Dr. Raker suggested, that we were not worried about the baby. In addition to the therapy mentioned in the protocol he received penicillin as an active form of treatment for the upper respiratory infection. At the time of operation we found what we hoped to find — namely, a lesion in the mesentery of the jejunum approximately at the midjejunum. This mass was pear-shaped, measured about 8 by 5 by 4 cm. and extended almost to the base of the mesentery. The vessels going into the intestine to which this mass was attached went along both sides of the mass. The mass appeared to be cystic. The intestine immediately below the mass and probably for 30 cm. did not appear to contain any gas. The intestine above the mass contained gas but was not overdistended. The intestine in the region of the mass appeared normal except where the mass was attached. In this region the intestine was being pressed upon by the tumor from below, partially occluding the lumen. The muscle coat of the intestine went through the mass for about 2 to 5 cm. and then became unrecognizable; it fanned out on the external surface of the mass. In an effort to learn what the disease was we attempted to separate the mass from the intestine, although we thought it was probably a duplication. We were able to demonstrate that there was a sharing of the muscle coat of the bowel and that the mucosa was intact. The cyst contained clear fluid. After the operation the patient did very well, and he was discharged from the hospital on the eleventh postoperative day.

DR. MORGAN: Dr. Crawford has described the gross appearance, size and shape of the cystic structure (Fig. 2), and he has mentioned that the mucosa of the jejunum was intact and that the muscle of the cystic lesion fanned out to join that of the wall of the jejunum. These several features, particularly the last two, are typical of duplication rather than a diverticulum, in which there would have been a simple outpouching of the mucosa and wall of the bowel. Microscopical examination showed the cyst to be lined by gastric mucosa, portions of which had sloughed off although there was no frank ulceration. In view of Dr. Crawford's statement that there was no communication between the lumen of the duplication and that of the jejunum and in the absence of any other source of bleeding, I am afraid we cannot attach too much significance to the single guaiac-positive stool reported at the time of admission.

This type of congenital lesion is very well covered by Gross,* who defines such duplications as spherical or elongated, hollow structures that possess a coat of smooth muscle, are lined by mucous membrane similar to some part of the alimentary canal and are intimately attached to some portion of the alimentary tube. They have been found at almost every level from the base of the tongue to the anus but are observed more commonly in relation to the small intestine than to any other part of the gastrointestinal

*GROSS, R. E. *The Surgery of Infancy and Childhood: Its principles and techniques.* 1000 pp. Philadelphia: Saunders, 1953.

tract. The mucosa lining the cyst may be of any type found in the gastrointestinal tract, and on occasion

FIGURE 2.

several types may be present. Usually, the cyst is filled with clear, colorless and mucoid fluid, which is secreted by the lining mucosa, and in some specimens the entrapped fluid has apparently been under enough pressure to have caused sloughing of the mucosa. Although some of the duplications have been found to communicate with the bowel, the majority are closed structures. In particular, duplications are to be distinguished from mesenteric cysts, which are lymphatic in origin, have a thin wall and can easily be peeled away from the adjacent viscera; duplications, on the other hand, usually require resection of the segment of bowel to which they are attached.

DR. ALLAN M. BUTLER: Since in such a patient as this the withdrawal of gastric juice by stomach tube and the administration of saline solution by intravenous infusion may result in hypochloremic and hypokalemic alkalosis and since appropriate multiple-electrolyte parenteral fluid therapy presents such undesirable metabolic disturbance I should like to know how much gastric fluid was withdrawn and what was the nature of the intravenous therapy?

DR. R. C. DARLING, JR.: Approximately 75 cc. a day was drained via the gastric tube. Administration of physiologic saline solution was started.

DR. BUTLER: Starting parenteral fluid as 0.5 per cent physiologic saline solution containing 5 to 10 per cent glucose is all right, but I hope that multiple electrolytes of about 75 milliequiv. of base per liter, of which potassium contributed about half the base, were given.

DR. DARLING: Multiple electrolyte solutions were given six hours before operation and postoperatively.

DR. CRAWFORD: We might add that the serum electrolytes were normal throughout the postoperative course on such a program.

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SURGICAL PILGRIMAGE

MORE than 500 surgeons from the United States and Canada attended the first overseas sectional meeting of the American College of Surgeons, held in London from May 17 to May 19, in conjunction with the Royal College of Surgeons. The larger gatherings of the congress took place in the new Great Hall of the College "with its English chestnut panelling, gurjun floor, and power-driven window blinds." Used for social occasions during the meetings was the new council chamber, panelled with oak veneer from a single tree planted at Northamptonshire in the reign of Elizabeth I, the gift to the College of Ethicon Suture Laboratories, Limited.

Among the Boston participants in the program were Dr. Arthur W. Allen, a former president of the College, who read a paper on the treatment of carcinoma of the colon, and Dr. S. F. Marshall, who spoke on cancer of the stomach. Dr. E. F. Cave discussed Sir Reginald Watson-Jones's paper on internal fixation of fractures, and Dr. R. H. Sweet discussed the paper of Mr. Philip R. Allison, of Leeds, on cancer of the esophagus. In the course of the proceedings the Moynihan Lecture was delivered by Dr. Walter C. MacKenzie, of Edmonton, Alberta, on acute pancreatitis, and the Hunterian Lecture by Dr. Howard C. Maffziger, of San Francisco, on progressive exophthalmos.

An interesting sidelight on the sturdy British character as well as on the subtle vagaries of specialization was the remark of Sir Gordon Gordon-Taylor, noted by the *British Medical Journal*, that he had performed his seventy-first hindquarter amputation on his seventy-sixth birthday. The record is vaguely reminiscent of James Norman Hall's charming series of stories on "Doctor Dogbody's Leg," which relates with the utmost authenticity the various episodes, each of which resulted in the loss of that eminent naval surgeon's larboard limb.

Although many of the congressionists had already attended meetings in Glasgow and Edinburgh and the annual meeting of the Association of Surgeons of Great Britain and Ireland, held in Leeds, and were planning to go on to similar gatherings in France, Belgium and Italy, their durability appeared to be unimpaired. They were still able to attend receptions at Lancaster House on behalf of the Government, at the House of Lords, the Society of Apothecaries and the Ciba Foundation and to face unshaken the ceremonial circumstance of a banquet at the Dorchester Hotel.

On account of the illness of President Fred W. Rankin, whose untimely death occurred in the very week of the meetings, Dr. Frank Glenn presided over the general sessions.

Again, the common cause of science and of humanitarianism has contributed cohesion to the bond between two countries whose political policies cannot always be made to agree.

FEDERAL AID AND HOSPITAL CONSTRUCTION

THE existing pattern of medical care in this country is based on a close personal relation between patient and physician, with the hospital a strengthening link between the two as a haven for the one and a workshop for the other. After World War II a deficit of hospital beds seriously limited this relation and the prospect of federal aid in construction of hospitals seemed to many a threat of socialized medicine. It is a significant accomplishment of the federal Government that the physical defect has been largely remedied without the intrusion of a paternalistic state in the function of what it helped to build. This contribution, as it applies to Massachusetts, is described elsewhere in this issue of the *Journal* by A. Daniel Rubenstein, director, Division of Hospitals, Massachusetts Department of Public Health.

Under the provisions of the Hospital Survey and Construction Act federal funds under state supervision were made available on a matching basis for hospital and health-center construction. In their first reaction to the program many physicians and hospital trustees considered the Act an actual encroachment of the Government on American medicine and saw in it the beginnings of state medicine. Subsequent events have shown that governmental aid could be accepted in this area without loss of control and with the freedom of both physician and hospital unimpaired. This has been general experience throughout the Commonwealth of Massachusetts, and medical care and hospital administrative facilities have been significantly improved.

As stated in Rubenstein's report, perhaps the primary reason for the absence of paternalism is the easy adaptability of the Act to the present scheme of medical care; it bolsters and does not interfere with patient-physician relations and has sought merely to improve facilities for medical care; it has encouraged many hospital trustees and staff physicians jointly to undertake building programs that would assuredly have been impossible without federal aid. One community was enabled to complete a hospital after a preliminary campaign for funds had resulted in only enough contributions to build the outside walls; no further progress had been made until a federal grant stimulated a second campaign for additional funds to finish the job.

The Hospital Survey and Construction Act is making a real contribution to facilities for medical care throughout the country. It has proved that the Government, physicians and hospitals can work together for the benefit of the citizen patient; it has demonstrated that governmental aid without interference can be accomplished in selected areas of medicine. It is probably significant that this particular area involved structures and not functions. Where there have been overlapping functions, as in the Veterans Administration, the going has been harder.

THE DROWNING SEASON

THE midvacation point, occurring at about this time, must also be regarded, with intelligent appraisal, as the peak of the drowning season. The fact that the peak occurs during the month of July has been confirmed by the statisticians of the Metropolitan Life Insurance Company, who find also that accidental drowning is to a considerable degree a sex-linked characteristic with male victims outnumbering females six to one.

Boys in their teens comprise the largest single group in the 6500 drownings that occur each year in the United States; swimming accounts for about half of the fatalities in this group, and boating accidents for a fifth. Children from one to nine fall into natural bodies of water or go beyond their depth while wading; very young children are drowned about the home in garden pools, cesspools, septic tanks, wells and cisterns.

Good advice concerns the danger of swimming alone and of long-distance swimming unaccompanied by a boat. It emphasizes the necessity of learning to swim well and of suitable behavior in boats, as well as of checking the condition of boats and of heeding weather warnings. Constant vigilance in watching over small children and the urgency of covering over or fencing in the danger spots hardly need be stressed.

A brewer was lately fined £30 in England for adulterating his beer with the grains of Paradise. *He deserved to be executed.*

Boston M. & S. J., *August 2, 1854*

MASSACHUSETTS MEDICAL SOCIETY

AMENDMENT TO GENERAL LAWS

Attention of all physicians is called to an amendment to Section 9 of Chapter 46 of the *General Laws* of Massachusetts, approved February 23, 1954, providing that the cause of death shall be *printed or typed on all death certificates.* The handwriting of the physician is no longer legally acceptable.

Physicians who do not print or type the causes of death on death certificates are causing costly and embarrassing delays in connection with the handling of funeral services by undertakers.

ROBERT W. BUCK, M.D.
Secretary

CIRCULAR OF ADVANCE INFORMATION

Fellows of the Society may receive copies of the *Circular of Advance Information for Councilors* if requests are received by the Secretary before August 6.

ROBERT W. BUCK, M.D.
Secretary

SQUEEZE BEFORE MAILING

Various postal districts in the Boston area report that the caps of from three to twelve cardboard mailing tubes containing specimens of blood or urine are lost each day, sometimes with unfortunate effect on other mail. No one likes to receive a letter or package stained with blood or urine.

Physicians, technicians and secretaries are urged to apply pressure along the middle of the tube with the thumbs and fingers of both hands. A tube of inferior composition will not withstand this test, and the contents will spill.

It is urged that physicians communicate with all laboratories supplying inferior tubes, emphasizing the necessity for safe packaging. All specimen tubes should be tightly corked, and the caps of mailing containers screwed on firmly before mailing.

ROBERT W. BUCK, M.D.
Secretary

CIVIL DEFENSE AGENCY

ROLE OF THE PHYSICIAN IN THE MEDICAL PROGRAM FOR CIVIL DEFENSE IN MASSACHUSETTS

When catastrophe strikes the role of the physician in disaster operations is vital. Civil defense is the preparation for and the carrying out of emergency functions for the purpose of minimizing and repairing injury and damage resulting from disasters caused by attack, sabotage or other hostile action or by fire, flood, earthquake or other natural causes. Specifically, the role of the medical and health services is briefly summarized for the convenience of the physician as follows:

The legislation upon which Civil Defense is based in Massachusetts is Chapter 639, Acts of 1950. Federal, State and Local Civil Defense Authorities have duties, powers and functions assigned to them by legislation to enable them to operate effectively in disaster.

Under the provisions of Executive Order No. 4, the Medical and Health Division of the Massachusetts Civil Defense Agency is established. The functions of the Medical and Health Division are to make preparations to provide the following services in the event of disaster, i.e. First Aid and Ambulance, Hospital and Medical, Communicable Disease and Biological Warfare, Blood, Laboratory, Chemical Defense, Vital Statistics, Mortuary, Health Supplies, Monitoring, Environmental Sanitation, Food and Nutrition.

Manuals of organization and operation of the twelve sections of the Medical and Health Division [First Aid and Ambulance Section, Hospital and Medical Section, Communicable Disease and Biological Warfare, Blood Section, Laboratory Section, Chemical Defense Section, Vital Statistics, Mortuary Section, Health Supplies Section, Radiological Monitoring Section, Environmental Sanitation Section and Food and Nutrition Section] have been published and are available to physicians. These manuals contain vital information regarding the nature and scope of the planning in many services provided for the care of casualties.

The total liabilities of the Commonwealth in the event of sudden disaster are determined by studies of expected casualty loads in critical target areas. These studies include not only the total casualty load expected from various types of thermonuclear weapons, but also a total of the types of injuries sustained among the surviving casualties. To meet this liability a study of existing medical personnel, facilities and equipment has been made. All public buildings of the Commonwealth that can be converted into hospitals have been surveyed and methods of expanding existing hospital facilities outside target areas have also been studied. Three hundred First Aid Stations have already been established in more than 100 cities and towns of the Commonwealth. Essential medical supplies are dispersed in storage at more than 30 other locations. Detailed information regarding this material will be made available upon request.

Close liaison is maintained by the Civil Defense Agency with the various professional organizations in the development of the Medical and Health program. The Massachusetts Medical Society, the Massachusetts Dental Society and other professional organizations have their own Civil Defense Committees which have contributed much to the medical program for Civil Defense.

Large numbers of technical personnel will have to be trained to meet the needs of disaster. Outlines of personnel training courses which may be undertaken in such programs are available in the *Manual of Personnel Training of the Medical and Health Division.*

Local universities, colleges and schools can give valuable assistance to Local Civil Defense Directors and their Medical and Health Staff in establishing training and other types of programs.

Hospitals may participate by periodically implementing their disaster plans in cooperation with the Local Civil Defense Organization, thus enabling their personnel to gain clear concepts of their duties and responsibilities in disaster.

Upon request symposia and lectures may be arranged by the Medical and Health Division of the Massachusetts Civil Defense Agency for various professional groups in the medical aspects of the Civil Defense program. Literature, films and other demonstration material are available for educational purposes upon request.

THOMAS F. MAHER, M.D., D.P.H.
Executive Medical Officer

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(Notices on page xi)

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NOTICES

SOCIETY MEETINGS AND CONFERENCES

AUGUST 13–23. Consultation Clinics for Crippled Children in Massachusetts. Page 1054, issue of June 17.
AUGUST 17–20. Argentine Congress of Thoracic Surgery. Page 708, issue of April 22.

CALENDAR FOR THE WEEK BEGINNING THURSDAY, AUGUST 5

THURSDAY, AUGUST 5
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.
*11:00 a.m. Thoracic Conference. Congenital Anomalies of the Thoracic Wall. Dr. Lance Bromley. Main Amphitheater, Peter Bent Brigham Hospital.

FRIDAY, AUGUST 6
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:30–11:30 a.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.
*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.
*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.
*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Waltham Street.

SATURDAY, AUGUST 7
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:30–10:00 a.m. Orthopedic Staff Conference, Boston City Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

MONDAY, AUGUST 9
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Medical and Surgical Clinic on Diabetic Foot Problems. New England Deaconess Hospital.
*8:30–9:30 a.m. Clinic by entire Surgical Staff and Anesthesia Staff. Cheever Amphitheater, Dowling Building, Boston City Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.

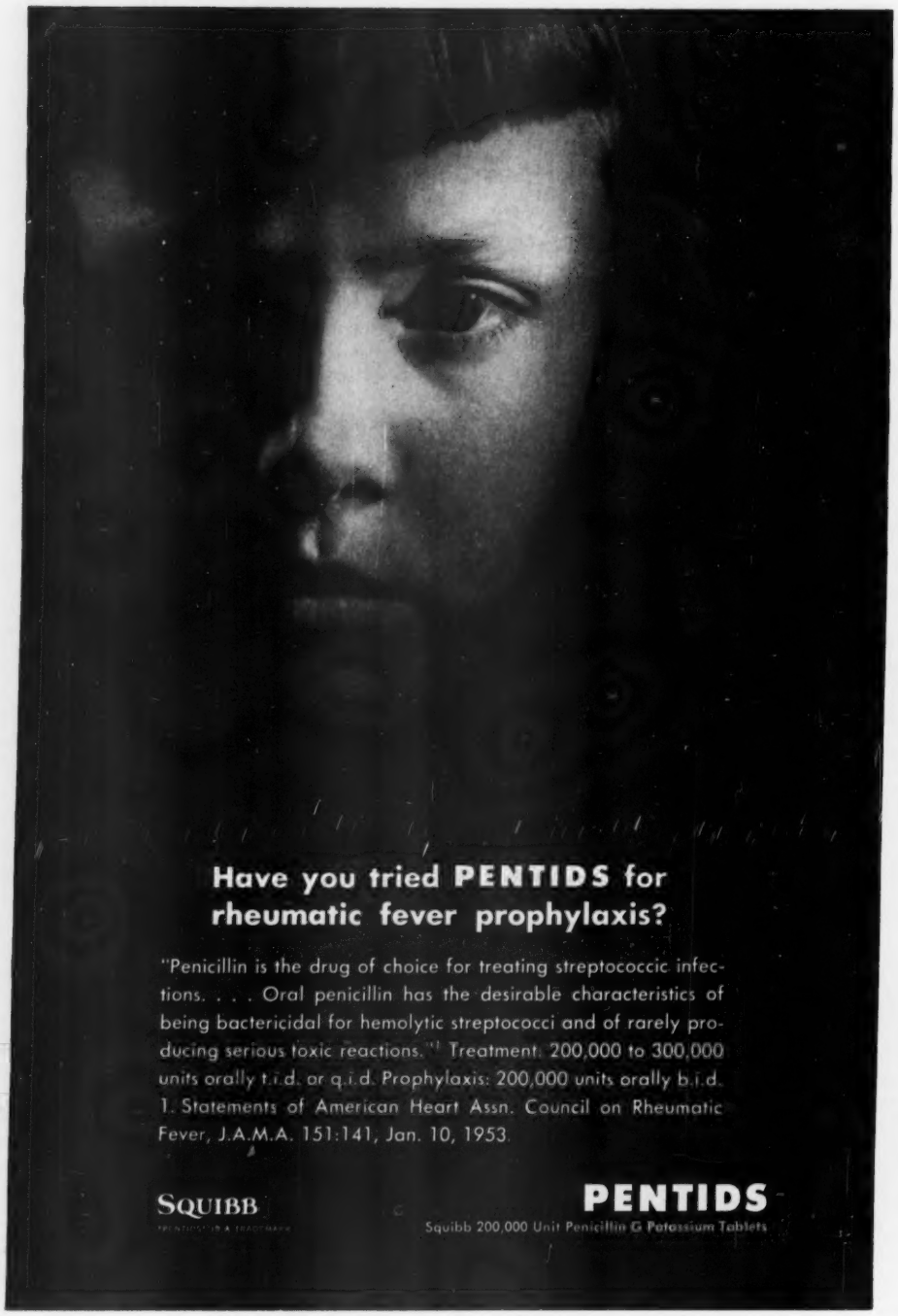
TUESDAY, AUGUST 10
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:00 a.m. Geriatrics Clinic. Peter Bent Brigham Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*12:00 m. Pediatric Grand Rounds. Cheever Amphitheater, Dowling Building, Boston City Hospital.
*12:15–1:15 p.m. X-Ray Conference. Dr. Merrill Sosman. Main Amphitheater, Peter Bent Brigham Hospital.
*5:00–6:00 p.m. Service Meeting followed by Clinical Conference (Medical, Surgical, Obstetrical). Faulkner Hospital.

WEDNESDAY, AUGUST 11
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m. Boston State Hospital Psychiatric Seminar. Reception Building Auditorium, 591 Morton Street, Dorchester.
*12:00 m.–1:00 p.m. Clinicopathological Conference. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*12:30 p.m. Weekly Pathological Meeting. Joslin Auditorium, New England Deaconess Hospital.
*12:30–1:30 p.m. Weekly Staff Review of Autopsies. Dr. William A. Meissner. Joslin Auditorium, New England Deaconess Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*1:00 p.m. Massachusetts General Hospital Hand Clinic. Out-Patient Department.
*2:00–3:00 p.m. Pediatric Conference for Practitioners. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*4:00–5:30 p.m. Fracture Lecture, Boston City Hospital.
*4:00–6:00 p.m. Overholt Thoracic Conference. Joslin Auditorium, New England Deaconess Hospital.
*6:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.

*Open to the medical profession.

Index to Advertisers

	PAGE
Abbott Laboratories	iv, v
Astra Pharmaceutical Products, Inc.	ix
Baldpate, Inc.	x
Bellows Farm	vi
Boston Medical Laboratory	vi
David Memorial Nursing Home	x
Electroencephalographic Laboratory, Inc.	vi
Glenside, Inc.	x
Hoffmann-La Roche, Inc.	After vi
Leary Laboratory	vi
Eli Lilly and Company	Front Cover
Maltbie Laboratories, Inc.	xiii
Perkins School	x
Ring Sanatorium	x
Sanborn Company	vii
Schenley Laboratories, Inc.	ii
Sharp & Dohme (Division of Merck & Co., Inc.)	Back Cover
Southern Medical Supply Co.	x
E. R. Squibb & Sons (Division of Mathieson Chemical Corporation)	xii
Storrow House (Massachusetts General Hospital)	vi
Warner-Chilcott Laboratories, Inc.	iii
Washingtonian Hospital	x
Westwood Lodge, Inc.	x
Winthrop-Stearns, Inc.	viii
Wiswall Sanatorium	x
Woodside Cottages, Inc.	x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1. Statements of American Heart Assn. Council on Rheumatic Fever, J.A.M.A. 151:141, Jan. 10, 1953.
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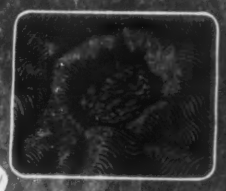

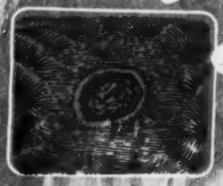

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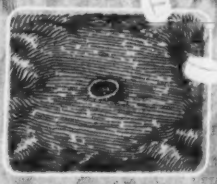

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1. Sulzberger, M.B. *et al.: J.A.M.A.* **151**: 468, Feb. 7, 1953
2. Smith, C. C.: *A.M.A. Arch. Dermat. & Syph.* **68**: 50, July, 1953

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